CHAPTER 8

Benjamin A. Alman
Michael J. Goldberg

Syndromes of Orthopaedic Importance

The word *syndrome* is derived from a Greek word that means *to run together*. When several relatively uncommon anomalies occur in the same individual, it may be nothing more than coincidence. However, if all the anomalies result from the same cause, or occur in the same pattern in other children, that particular combination of birth defects is called a *syndrome*. A syndrome should be suspected if a characteristic orthopaedic malformation (e.g., radial clubhand) is encountered, if all four extremities are affected, if limb deformities are symmetric, if there are several associated nonorthopaedic anomalies, or if the patient has a familiarly dysmorphic face. Children who have syndromes look more like one another than like their parents (1–4).

It is not unusual for an orthopaedist to be the first physician to recognize that a child has characteristics of a syndrome. In such cases, appropriate referrals should be made to a geneticist to assist in syndrome identification, order appropriate confirmatory tests, and arrange for management of the nonorthopaedic manifestations of the syndrome. The evaluation of a child for a syndrome includes a family history, a systems review, and a search for minor dysmorphic features, such as abnormal palm creases or abnormal shape of digits or toes. These evaluation processes may not be of immediate orthopaedic importance, but they are the clues to look further.

During fetal development, cell signaling pathways are activated in a coordinated manner to allow cells to divide, differentiate, move, and die off, ultimately resulting in a normally formed individual. These cell signaling pathways play roles in the development of multiple organs. It is not surprising that dysregulation of such developmentally important pathways can cause the malformation of a number of organs, resulting in several otherwise uncommon abnormalities occurring together, producing a syndrome. Such pathways can be dysregulated by a mutation in a key pathway member, by fetal environmental factors (e.g., a teratogen, such as in fetal alcohol syndrome), or both.

The relation between the clinical (phenotypic) features and the cause of a syndrome is not always as simple as one would wish. Even within a family in which all the members carry the identical causative gene mutation, some individuals are minimally affected, whereas others have all of the findings of the syndrome. This may be due to the presence of modifying genes, which may not be inherited in the same way as the gene mutation that causes the syndrome, or due to fetal environmental factors that modify the manner in which the pathways are activated. In addition, different mutations in the same gene can cause different syndromes, because the products of different mutations have different cellular functions. Such is the case with the dystrophin gene, which causes both Duchenne and Becker muscular dystrophies.

Information about the etiology of a syndrome is important, because it has implications for the parents as to the risk of recurrence in subsequent pregnancies, and may hold the key to the development of novel treatments. The rapid pace of basic research in developmental biology and genetics makes it difficult for a traditional textbook to provide the most up-to-date information about syndrome etiology. The Internet is becoming an excellent source for such information. One useful site is the On-line Mendelian Inheritance in Man (OMIM), administered by the National Institutes of Health. This site can be accessed at http://www.ncbi.nlm.nih.gov/Omim/ and can be searched by syndrome name, causative gene, or clinical findings (5).

The care of children with syndromes involves multiple specialists (6). Discussions about the risk of subsequent pregnancies are in the realm of the genetic counselor. While parents often assume that if the condition has a name, it is treatable or curable, this sadly, is not the case. The importance of understanding syndromes is in recognizing associated medical abnormalities that may be life threatening, adversely influence orthopaedic outcomes, or may influence surgical timing and management. Importantly, patients can come to significant harm if an orthopaedist misses recognizing a syndrome. For instance, in the case of Marfan syndrome, starting a child on beta-blockers can prevent a catastrophic cardiovascular event.

Even if parents are not planning subsequent pregnancies, and if there are no plans for their child to undergo surgery in the near future, genetic evaluation is still important for proper syndrome diagnosis. Correct diagnoses are essential for research into syndrome etiology and treatment. Patients should be given the opportunity to participate in such research, especially in cases of relatively rare syndromes.

Nomenclature can confuse syndrome identification, because a single syndrome may have several names. Eponyms are not descriptive of the syndrome, nor do they give information about etiology. Many syndromes are caused by a mutation in a gene, and the causative gene has been identified in most such syndromes. Classifying syndromes by the causative gene alone can be problematic because some genes cause more than one syndrome, some syndromes are caused by more than one gene, and some syndromes are not caused by a gene mutation. Furthermore, gene names are frequently unrelated to clinical findings associated with a given syndrome. A numbering system is used by computer databases; the most widely used is that of the OMIM (5), but this is helpful only for database searches. An ideal nomenclature, which would give information about clinical findings and etiology, has yet to be developed.

Knowledge of the genetic cause of syndromes does not supplant the need for the clinician to know the phenotypic features of individual syndromes (7). For many syndromes, molecular genetic tests are not available or are available only at a very high cost. As such, it is impractical to test a given patient for every known genetic condition (8). A thorough study of the patient's history and a physical examination gives clues as to which supportive tests to order, such as radiographs. This information is used for narrowing down the diagnosis to only a handful of syndromes. In many cases, the ultimate diagnosis can be made on the clinical and radiographic findings alone [e.g., neurofibromatosis (NF) type I]. For syndromes in which molecular genetic tests are available, these are usually performed to confirm a diagnosis rather than to make a diagnosis and should only rarely be ordered by an orthopaedist before consultation with a clinical geneticist or genetic counselor.

It is clinically useful to classify syndromes caused by gene mutations into groups broadly categorized by the function of the causative gene (9, 10). Such syndromes can be broadly classified into those caused by mutation in genes encoding one of the following types of proteins: structural proteins, proteins that regulate developmentally important signaling pathways, proteins implicated in neoplasia, proteins such as enzymes that play a role in processing molecules, and proteins that play a role in nerve or muscle function (7). Syndromes within each broad group share similarities in the mode of inheritance and clinical behavior. For instance, syndromes caused by mutations in genes encoding structural proteins tend to be inherited in an autosomal dominant manner and result in skeletal structures that wear out with time, for which corrective surgery has a high recurrence or failure rate. Most of the disorders in this chapter are grouped using this functional genetic scheme. The one exception is contracture syndromes, which are considered as a separate group. Although the genetic etiology of many of the contracture syndromes has been identified, it is easiest, from a practical standpoint, to consider them as a few subgroups based on clinical and treatment similarities.

STRUCTURAL GENES

A variety of proteins play important roles in the connective tissues, including the bones, articular cartilage, ligaments, and skin. Mutations in such genes disrupt the structural integrity of the connective tissues in which they are expressed. In most cases, the phenotype is absent or there are only minor manifestations present at birth; the phenotype evolves with time, because the abnormal structural components slowly fail or wear out with time as the individual grows. Deformity often recurs after surgery, because the structural components are abnormal and will wear out again. In cases where the structural abnormality involves cartilage, there may be growth abnormality caused by physeal mechanical failure or early degenerative disease of the joints caused by articular cartilage failure. When a protein that is important for ligament or tendon strength is affected, joints often subluxate. There can be substantial heterogeneity in the severity of the phenotype, depending upon the exact way in which the mutation alters the protein function. In patients with mild disease, life expectancy is normal; however, in patients with more severe disease, life expectancy may be shortened because of secondary effects of the structural defects on vital organs. These disorders tend to be inherited in an autosomal dominant manner (9, 10). Many of the disorders caused by mutations in genes that encode structural proteins, including osteogenesis imperfecta and spondyloepiphyseal dysplasia, are covered in other sections of this textbook.

Marfan Syndrome. Anton Marfan, a French pediatrician, first described this syndrome in 1896, as a condition associated with long limbs and involvement of the cardiovascular, ocular, and skeletal systems (11). Although some authorities believe that Abraham Lincoln had Marfan syndrome, there remains considerable controversy surrounding this, and a decision was made against using DNA from his remains to test for this diagnosis (12). This is one of the few syndromes caused by a mutation in a gene encoding a structural protein that is associated with tall stature. Patients can be recognized by the characteristic tall stature, arachnodactyly (abnormally long and slender digits), dolichostenomelia (long, narrow limbs), pectus deformities, and scoliosis. Stria can be seen in the skin (Fig. 8-1). There are a number of cardiovascular anomalies associated with this condition, including aortic regurgitation, aortic dilatation, aneurysms, and mitral valve prolapse. Ocular findings are myopia and superior displacement of the lens. The lens moves in the opposite direction in homocystinuria, a condition that sometimes is misdiagnosed as Marfan syndrome. Undiagnosed patients with Marfan syndrome not infrequently present to an orthopaedist with a diagnosis of scoliosis. It is

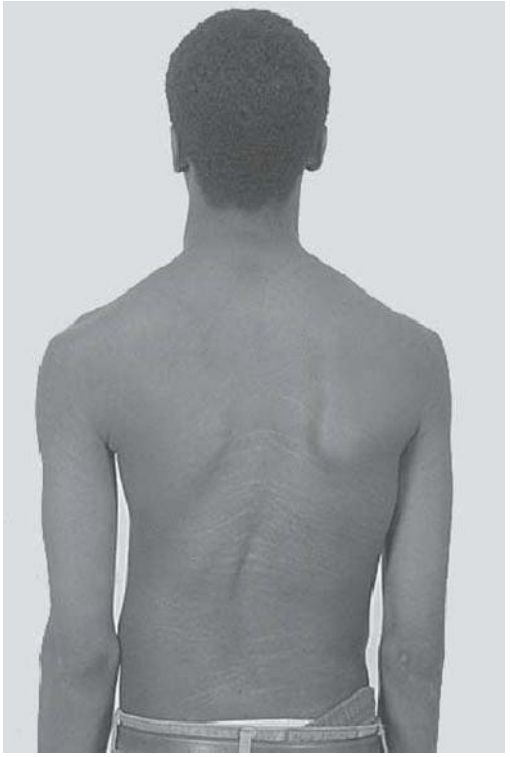


FIGURE 8-1. Stria in a boy with Marfan syndrome, who initially presented for evaluation of scoliosis.

important for an orthopaedist to recognize this condition, since its identification allows for referral for management of the cardiovascular abnormalities, early treatment of which can prevent premature mortality.

Diagnosis and Physical Findings. The diagnosis is made on the basis of family history and clinical findings, including abnormalities in the ocular, cardiac, and musculoskeletal systems (13). Despite several meetings to develop a consensus about diagnostic criteria, controversy remains as to the best set of diagnostic criteria to employ. If one uses more stringent criteria, this will exclude many individuals who are currently managed as Marfan syndrome patients. The less stringent Berlin criteria and the more stringent Ghent criteria are outlined in Table 8-1 (14–16). To further confound issues of clinical diagnosis, there is controversy about the definition of dural ectasia. The initial definition included a number of morphologic characteristics, as well as a dural volume >7 cm^3 below the inferior L5 endplate, as measured using a magnetic resonance image (MRI) study (14, 15). The normal dural volume in younger, growing children is not known, and the reliability and reproducibility of volume measures when used outside of clinical investigative groups is also unclear. A recent retrospective analysis suggests that a sagittal dural sac width at S1 greater than that at L4 is a better criterion for dural ectasia in children, adolescents, and young adults (16).

There are a variety of additional physical findings that are suggestive of Marfan syndrome and while not part of the diagnostic criteria, should alert one to consider this diagnosis. It was thought that the physical finding of an arm span longer than height would be diagnostic of Marfan syndrome; however, population studies have shown that this is not the case. The ratio of upper segment (head to pubic symphysis) to lower segment (pubic symphysis to plantar surface), which is normally 0.93 in a mature individual, is often decreased in Marfan syndrome to 0.85 or less (17). Two clinical findings associated with arachnodactyly are a thumb that protrudes past the ulnar border of the hand when it is held in a clenched fist (Steinberg sign) and overlap in the thumb and index finger when they are wrapped around the opposite wrist (18).

Radiographic Findings. Although there are a variety of radiographic findings that are frequently present in patients with Marfan syndrome, none are pathopneumonic. Spinal morphology suggestive of dural ectasia and pedicle dysplasia are suggestive of this disorder. The use of measurements from spine radiographs in making this diagnosis (an interpedicular distance at L5 ≥ 36.0 mm; a sagittal diameter at L5 ≥ 13.5 mm; a transverse process-to-vertebral width ratio at L3 ≥ 2.25 mm) yields a high sensitivity but a relatively poor specificity (16). A arachnodactyly is defined on radiographs as an increase in the ratio of length to width of the second to the fifth metacarpals (Fig. 8-2). The average ratio of the lengths of the second to the fifth metacarpals, divided by the widths of the respective diaphyses, is >8.8 in male patients and >9.4 in female patients with Marfan syndrome (19). There are no studies, however, that determine the sensitivity and specificity of the use of these measures to make a diagnosis of Marfan syndrome.

Etiology. Marfan syndrome is inherited in an autosomal dominant manner and is caused by mutations in the fibrillin gene (20). Like many inherited genetic disorders, almost a third of cases are sporadic due to a new mutation at embryogenesis. The expression of the mutant gene product inactivates the function of the normal gene product, an effect that is termed *dominant negative*. As such, this condition could potentially be treated by the use of therapies that decrease the expression of the mutant gene (21). The fibrillin protein plays a role in maintaining the normal mechanical properties of the soft tissues, especially in resistance to cyclic stress (22). The clinical findings of laxity and subluxation of the joints, and weakening of arterial walls with resultant aortic dilatation, are easy to understand on the basis of the function of fibrillin. The tall stature and arachnodactyly associated with the syndrome are seemingly difficult to attribute to the fibrillin mutation. However, the extracellular matrix also contains growth factors, which are bound to extracellular matrix proteins. Fibrillin mutations cause some of these extracellular growth factors, such as transforming growth factor β, to become more readily accessible to cell receptors (23). The increased growth factor availability likely causes increased cellular growth and rapid longitudinal bone growth; resulting in long, thin fingers and toes and tall stature. This raises the possibility that growth factor activity modulation could be used to treat some of the sequelae of Marfan syndrome (23).

TABLE 8-1 Diagnostic Criteria for Marfan Syndrome: A Comparison of the Berlin and Ghent Diagnostic Criteria

Berlin

If the patient has an affected first-degree relative, at least two systems of any class must be involved. In the absence of an affected first-degree relative, involvement of the skeleton as well as one major system and two minor systems are required.

Major Involvement	*Minor Involvement*
Ocular system	Skeletal system
Cardiovascular system	Ocular system
Dural ectasia	Cardiovascular system
	Pulmonary system
	Skin
	Central nervous system

Ghent

Diagnosis requires two major involvements and one minor involvement

Major Involvement	*Minor Involvement*
Family history or molecular data	Skeletal system
Cardiovascular system	Ocular system
Dural ectasia	Cardiovascular system
Skeletal system	Pulmonary system
Ocular system	Skin

Skeletal system

Presence of at least four of the following manifestations

Major Involvement	*Minor Involvement*
Pectus carinatum	Pectus excavatum of moderate severity
Pectus excavatum requiring surgery	Joint hypermobility
Reduced upper to lower segment ratio or arm span to height ratio >1.05	Highly arched palate with crowding of teeth
Wrist and thumb signs	Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
Scoliosis of >20 degrees or spondylolisthesis	
Reduced extension at the elbows (<170 degrees)	
Medial displacement of the medial malleolus causing pes planus	
Protrusio acetabula of any degree (ascertained on radiographs)	

Ocular System

Major Involvement	*Minor Involvement*
Ectopia lentis	Abnormally flat cornea (as measured by keratometry)
	Increased axial length of globe (as measured by ultrasound)
	Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

Cardiovascular System

Major Involvement	*Minor Involvement*
Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva	Mitral valve prolapse with or without mitral valve regurgitation
	Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 yr
Dissection of the ascending aorta	Calcification of the mitral annulus below the age of 40 yr
	Dilatation or dissection of the descending thoracic abdominal aorta below the age of 50 yr

Pulmonary System

Major Involvement	*Minor Involvement*
None	Spontaneous pneumothorax
	Apical blebs (ascertained by chest radiographs)

TABLE 8-1 *(continued)*

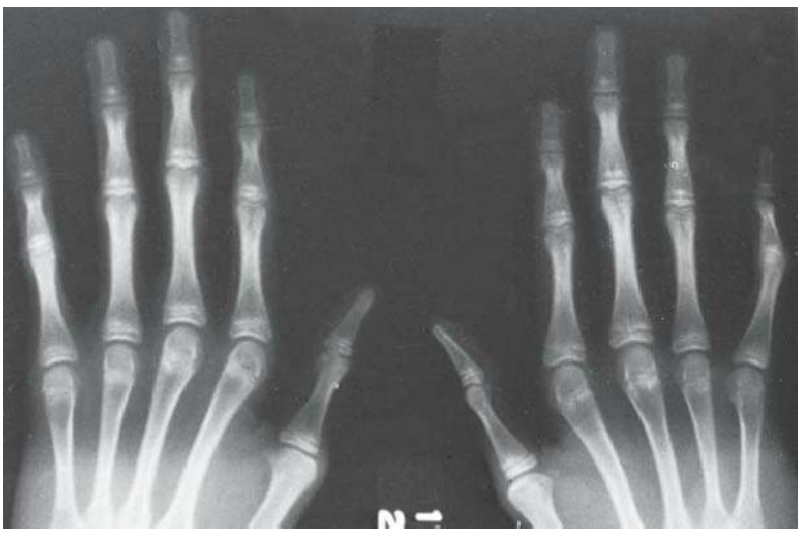
Skin and Integument	
Major Involvement	***Minor Involvement***
None	Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy, or repetitive stress Recurrent or incision hernias
Dura	
Major Involvement	***Minor Involvement***
Lumbosacral dural ectasia by CT scan or MRI	None
Family/Genetic History	
Major Involvement	***Minor Involvement***
Having a parent, child, or sibling who meets these diagnostic criteria independently Presence of a mutation in *FBN1* known to cause the Marfan syndrome Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	None

CT, computed tomography; MRI, magnetic resonance imaging.

Although molecular diagnosis for a mutation in the fibrillin gene is available, this is usually not required in making the diagnosis, as physical findings and information from radiographic studies are generally sufficient for this purpose.

Orthopaedic Manifestations and Their Management. Hyperlaxity is responsible for many of the clinical problems in Marfan syndrome, including subluxation of joints, a predisposition to sprains, and scoliosis. Scoliosis is a common reason for which patients are referred to the orthopaedist. Smaller curves can be managed in a manner similar to that for idiopathic scoliosis, with bracing considered for select curves in skeletally immature individuals. Although bracing is often prescribed, it seems to be less effective than in idiopathic scoliosis (24). This has led some to suggest that bracing only delays the need for surgical treatment. There are no well-controlled studies comparing brace treatment with observation or any other type of management in these patients. Although the efficacy of brace treatment remains controversial, we offer brace treatment using the same principles as for idiopathic scoliosis. Curves will often be relatively short and associated with deformity of vertebrae termed *dysplastic* (Fig. 8-3). The spinal deformity is often associated with kyphosis, especially in the lumbar spine region. Surgery is considered for rapidly progressive curves in skeletally immature individuals, or for large curves in skeletally mature individuals. Patients with Marfan syndrome have higher complication rates when undergoing scoliosis surgery than in idiopathic scoliosis. Infection, instrumentation fixation failure, pseudarthrosis, or coronal and sagittal curve decompensation occur in 10% to 20% of patients. Infection is often associated with a dural tear. Perioperative death from valvular insufficiency has been reported. To avoid such complications, the cardiopulmonary condition of patients with Marfan syndrome should be evaluated preoperatively (25–32). Overcorrection can also cause cardiovascular complications, and

FIGURE 8-2. Hands showing arachnodactyly. Notice the long, thin metacarpals and phalanges.



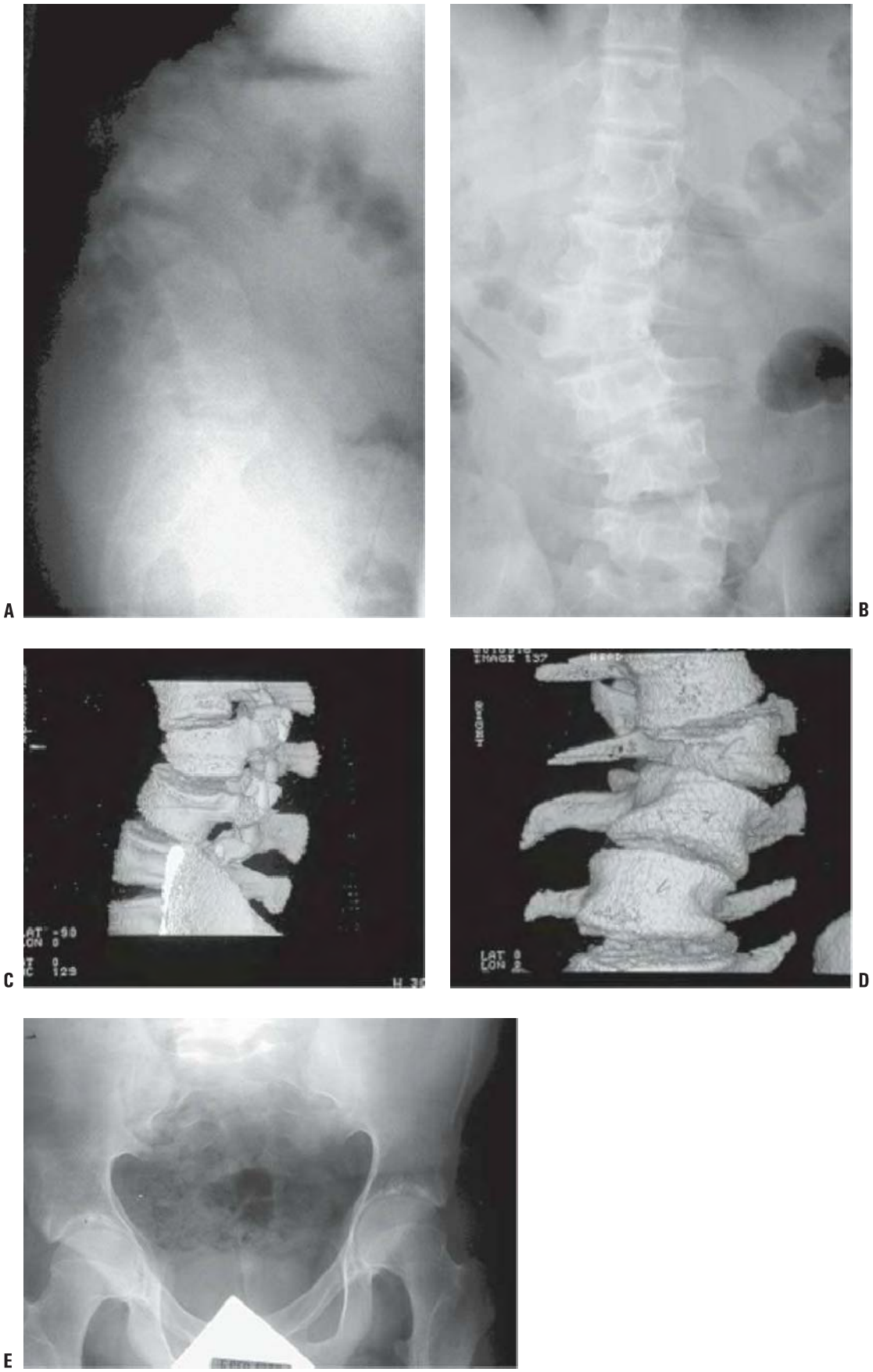


FIGURE 8-3. Scoliosis **(A,B)** and protrusia of the hips **(E)** in a patient with Marfan syndrome. **C, D:** Deformity of the apical vertebrae is shown in a three-dimensional reconstruction of a computerized tomographic scan image. (Courtesy of Chris Reily, MD, Vancouver, British Columbia, Canada.)

reducing the amount of correction in a patient treated with a growing rod was shown in a case report to reverse cardiac failure (33). Computerized tomography (CT) scan to assess bony anatomy, especially of the pedicles, is quite useful in preoperative planning of hook and screw placement. Other unusual spinal deformities can occur, such as subluxation of vertebrae (25, 34). Traction should be used with caution, especially in cases with underlying kyphosis, as it can worsen and cause subluxation (26).

Dural ectasia is common in individuals with Marfan syndrome and seems to increase in severity with age. Its severity is not related to the severity of other clinical findings; for instance, there is no association between aortic dilatation and dural ectasia (27). Although there is a slightly higher incidence of back pain in patients with dural ectasia than in those without, a 40% incidence of back pain in patients with Marfan syndrome without dural ectasia suggests that dural ectasia itself is not the cause of the pain. One should thus evaluate patients with Marfan syndrome for other causes of back pain even in the presence of dural ectasia.

Mild osteopenia is associated with Marfan syndrome; this may be caused in part by the fibrillin abnormality disrupting the normal extracellular matrix structure of bone, and in some cases it may be related to relative physical inactivity. Susceptibility to fracture does not seem to be a problem, and it is therefore not clear whether intervention for the decreased bone density is warranted (28, 29). Protrusio acetabula is present in about one-third of patients with Marfan syndrome. The radiographic diagnosis can be difficult as there is a deformity of the inner aspect of the pelvis that can distort the normal pelvic landmarks. Protrusion is not related to bone mineral density and is usually asymptomatic (30). Although prophylactic fusion of the triradiate cartilage is reported, for these reasons it is not warranted in the majority of cases.

Nonorthopaedic Manifestations. Cardiovascular failure can lead to premature death in patients with Marfan syndrome. Indeed, many cases of sudden death during athletic activities in the young are in individuals with Marfan syndrome. Despite this, there are no universally accepted criteria for restricting physical activity in individuals with Marfan syndrome. Early intervention using β-blockers can reduce the development of aortic dilatation. New treatments based on reversing the changes associated with the identified mutation are under investigation and will likely change the course for patients with Marfan syndrome. For instance, the antihypertensive agent, Losartan, has also been found to down-regulate the expression of transforming growth factor beta; animal studies as well as small clinical series suggest that its use can slow the progression of the cardiovascular side effects of this condition (23). However, larger scale clinical trials are required before routine use is recommended. Individuals with aortic dilation may also benefit from earlier cardiac surgical intervention. Lens dislocation requires ophthalmologic intervention. In Marfan syndrome the lens is dislocated in a superior direction, whereas in homocystinuria there is an inferior dislocation. Homocystinuria shares many clinical features with Marfan syndrome but is also associated with a coagulation disorder. As such, it is crucial that an individual suspected of having Marfan syndrome be evaluated for cardiovascular problems, and that the possibility of homocystinuria be excluded before the patient undergoes surgery.

Homocystinuria. It is important for the orthopaedist to be able to distinguish patients with homocystinuria from those with Marfan syndrome, as patients with homocystinuria often present to the orthopaedists with a clinical picture suggesting Marfan syndrome. Unlike Marfan syndrome, homocystinuria is associated with a coagulopathy, which can be fatal if unrecognized, especially during surgery. Although homocystinuria is not caused by a mutation in a gene encoding a structural protein, it shares phenotypic similarities with Marfan syndrome, and it is therefore being discussed here. It is caused by a defect in one of the enzymes that is important in the production of cysteine from methionine, thereby resulting in the accumulation of intermediate metabolites in the blood (homocysteine and homocystine) and in the urine (homocystine) (31, 32). There are several subtypes, and patients with type I have a phenotype similar to that of Marfan syndrome (35). Affected individuals are tall with long limbs and may have arachnodactyly and scoliosis. Dislocation of the lens of the eye is common but in contrast to Marfan syndrome the displacement is inferior. Osteoporosis is often more severe in type I homocystinuria than in Marfan syndrome. Vertebral osteoporosis can produce biconcavity and flattening of vertebral bodies, whereas in Marfan syndrome the vertebral bodies are either normal or excessively long. Widening of the epiphyses and metaphyses of long bones is more typically seen in homocystinuria. Mental retardation is not a feature of Marfan syndrome, but occurs in approximately half of all patients with homocystinuria (36). Patients with type I homocystinuria have an abnormality in clotting, which leads to venous and arterial thromboembolic episodes (37). Such episodes can complicate surgery, and as such a hematology consultation should be considered when planning surgery.

Type I homocystinuria is caused by a deficiency of cystathionine synthetase, which normally catalyzes the chemical union of homocysteine and serine to form cystathionine. The enzyme uses pyridoxine (vitamin B_6) as a cofactor. Blood levels of methionine are increased, and thus screening of patients with Marfan syndrome for homocystine in the urine (with the cyanide nitroprusside test) can differentiate type I homocystinuria from Marfan syndrome. Type II and III homocystinuria are biochemically distinct. Because the errors cause blocks at other points, blood levels of methionine are normal, and other clinical findings such as skeletal changes and thromboses are absent.

The treatment for homocystinuria depends on the type. In type I, the typical course is methionine restriction and pyridoxine supplementation (37). For types II and III, methionine restriction is harmful. Treatment with cofactors also varies for these other types. Vitamin B_{12} is suggested in the management of type II, and folic acid for type III.

Ehlers-Danlos Syndrome. Ehlers-Danlos syndrome (EDS) is a collection of different disorders that are associated with the common phenotypic findings of hyperextensibility of the skin and hypermobility of the joints. Easy bruisability of soft tissue, fragility of bone, calcification of soft tissues, and various degrees of osteopenia are associated with the various subtypes. The hyperlaxity allows affected individuals to have impressively large ranges of motion of the joints. Contortionists are often individuals with this syndrome. Although Tschernogobow first described the syndrome in 1892, the condition derives its name from reports by Edward Ehlers, a Danish dermatologist, in 1901, and Henri-Alexandre Danlos, a French physician, in 1908. These two individuals combined the pertinent features of the condition to provide a detailed description of the phenotype (38).

The main features of classic EDS are loose-jointedness and fragile, bruisable skin that heals with peculiar "cigarette-paper" scars and may show changes resulting from multiple bruises (Fig. 8-4). Children with this condition may be born prematurely because of premature rupture of fetal membranes, because these membranes are derived from the fetus itself. The fragile soft tissues can also cause problems such as "spontaneous" carotid-cavernous fistula, ruptures of large vessels, hiatus hernia, spontaneous rupture of the bowel, diverticula of the bowel, rupture of the colon, aortic dilatation, and retinal detachments (39–43).

Classification and Etiology. The tradition classification of EDS into 11 types (44) has been modified in a way that groups individuals with this disorder into 6 major types (45), based on clinical findings, genetic cause, and inheritance pattern (45) (Table 8-2). There additional subtypes of EDS, but these are very rare, often being reported as a single family. Although an understanding of the genetic cause of the rare types provides important information about how various proteins contribute to the maintenance of the mechanical integrity of the soft tissues, the infrequency of their occurrence makes their incorporation into a general classification scheme less useful to the clinician.

EDS is caused by mutations in either a collagen gene or in a gene that produces a protein that processes collagen. The types of EDS that are caused by a mutation in collagen are inherited in an autosomal dominant manner, whereas those caused by a protein processing defect (kyphoscoliotic and dermatosparaxis types) are inherited in an autosomal recessive pattern. Since collagen is the main structural component of a variety of connective tissues, it is easy to understand how these mutations cause the associated changes in soft-tissue mechanics (38, 46, 47).

There are several characteristics that are unique to the individual subtypes (48–50). The hypermobility type, which is characterized by multiple dislocations of joints, is also associated with a delay in achieving developmental milestones, perhaps because of the dislocations. Individuals with this type have the greatest functional disability. The vascular type is associated with ruptures of vessels or viscera. Such events are rare in childhood, but by the age of 20, one-fourth of those with the condition will have had some vascular or visceral complication. Teenage boys may be at a higher risk for this during their prepubertal growth spurt (51). Early death occurs, most commonly because of vascular rupture, with the median age of survival being <50 years. Individuals with the kyphoscoliosis type often present as "floppy" infants, and this diagnosis should therefore be considered in such children. Although molecular diagnosis is possible for some of the subtypes, these are usually not needed for making the diagnosis, and referral to clinical geneticists is usually sufficient to confirm a diagnosis. There are no universally accepted criteria for restricting participation in physical activity in patients with EDS, so recommendations to limit activity should be made on an individual basis.

Orthopaedic Manifestations and Management. Subluxations and recurrent dislocations of joints are common occurrences in the various subtypes. The chronic pain that such individuals complain of is often attributed to these subluxations. The management of the subluxations is problematic, and a multidisciplinary effort, including pharmacologic and

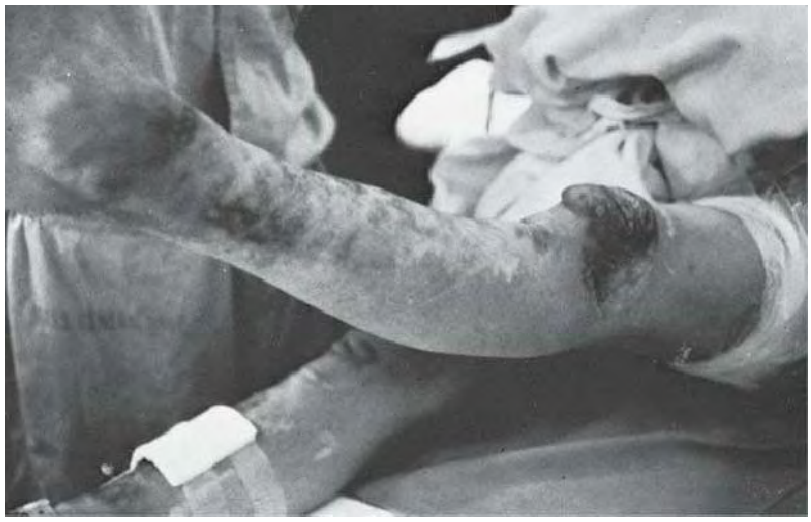


FIGURE 8-4. Patient with Ehlers-Danlos syndrome, type I. The knees and the pretibial regions have been subjected to recurrent injury and have accumulated heme pigmentation. (Courtesy of Michael G. Ehrlich, MD, Providence, Rhode Island.)

TABLE 8-2 A Modified Classification Scheme for Ehlers-Danlos Syndrome

New	Former	Major Clinical Findings	Minor Clinical Findings	Genetic Etiology
Classic	Type I Type II	Skin hyperextensibility Wide scars Joint hyperlaxity	Smooth skin (velvety) Complications of joint hypermobility Easy bruisability Tissue fragility and extensibility resulting in hiatal hernia, anal prolapse, or cervical insufficiency Family history	*COL5A1* mutations
Hypermobility	Type III	Skin hyperextensibility Smooth velvety skin Generalized joint hypermobility	Recurrent joint dislocations Chronic joint dislocations Family history	Unknown
Vascular	Type IV	Thin, translucent skin Arterial, intestinal, or uterine rupture or fragility Excessive bleeding	Hypermobility of small joints Tendon or muscle rupture Clubfoot Varicose veins Arteriovenous or carotid-cavernous fistulas Pneumothorax Hemothorax Family history History of sudden death in family	*COL3A1* tenascin-XB
Kyphoscoliosis	Type VI	Generalized joint laxity Hypotonia at birth Progressive infantile scoliosis Scleral fragility Rupture of the ocular globe	Tissue fragility Easy bruisability Arterial rupture Marfanoid habitus Microcornea Osteopenia Family history	Lyslhydroxlyase deficiency
Arthrochalasia	Type VIIA	Severe generalized hypermobility	Skin hyperextensibility Tissue fragility	*COL1A1* or *COL1A2* mutations
	Type VIIB	Congenital hip dislocation	Easy bruisability Muscle hypotonia Kyphoscoliosis Osteopenia	
Dermatosparaxis	Type VIIC	Severe skin fragility Sagging, redundant skin	Soft doughy skin texture Easy bruising Premature fetal membrane rupture Hernias	Procollagen 1 *N*-terminal peptodase

physical therapeutic approaches, is often required. As opposed to individuals with normal joint laxity, patients with this condition have patellar instability in multiple planes (39). Since the matrix components that provide the mechanical properties to the soft tissues are defective, surgical approaches focusing on ligaments and tendons (e.g., soft-tissue procedures around the shoulder) have a low success rate. A variety of such operations are reported, such as osteotomies, which change the direction and location of insertion of tendons or osteotomies or that provide a larger joint area (tibial tubercle transfer operations for patellar dislocations, and femoral and pelvic osteotomies for hip subluxation). Procedures that involve surgery to the bones have a higher success rate than operations on ligaments or tendons. In particularly problematic cases, it may be necessary to place a bone graft to limit motion and prevent dislocation (e.g., a posteriorly placed graft at the elbow). Arthrodesis may be required as a last resort in those cases that remain symptomatic despite other managements (52–54).

Scoliosis is common in EDS, and is usually managed using the same principles as those for idiopathic scoliosis, although there is a lack of studies investigating the implications of scoliosis in this population and the efficacy of this management approach. Surgical management can be problematic in the vascular type, as there are a number of complications, and vessel ruptures can occur during surgery (41, 55). It is important not to place undue stretch on vessels during surgery, and it is probably safest to have a vascular surgeon available in case a major disruption is encountered. Spondylolisthesis can occur, and it

may be present at multiple levels, including nonadjacent sites (42). Valve problems can occur in EDS, so patients should have a cardiac evaluation before undergoing surgery. Low bone density is identified in EDS; however, when one corrects for the activity level of these patients, the bone density may not be so abnormal (56). Pharmacologic treatment for low bone density should be considered only in rare instances.

OVERGROWTH SYNDROMES AND CONDITIONS CAUSED BY TUMOR-RELATED GENES

There are a variety of cellular proteins and signaling pathways that are important in regulating cell reproduction or proliferation. A mutation that results in dysregulation of such pathways can increase cell proliferation, resulting in overgrowth of a cell type or an organ. Such pathways are frequently dysregulated in neoplasia. In some inherited conditions, when a single copy (one allele) of a gene that is important in regulating cell proliferation is mutated in the germ line, the result is an overgrowth phenotype, but when the second copy becomes mutated in a somatic manner (in a certain cell type), the result is the development of a tumor. Since these disorders are usually caused by one copy of the defective gene, they tend to be inherited in an autosomal dominant manner. The type of tissue or organ involved depends on the cell type in which the gene is expressed. In many syndromes, such as NF, the tissues of the musculoskeletal system are affected, resulting in obvious bone or soft-tissue abnormality. There is a risk of malignant progression, which develops over time as the cells are subjected to genetic damage (second hit), causing the loss of the normal copy of the causative gene. Recurrence of a deformity after surgery is not unusual, because the underlying genetic defect that causes abnormal cell growth cannot be corrected by any surgical procedure. Many children present with limb-length discrepancy, but most of these conditions will not be related to a syndrome and can be managed as described in Chapter 28 on limb-length inequality. It is important to understand the various associated syndromes so that appropriate referrals can be made for nonorthopaedic problems.

Neurofibromatosis. There are several forms of NF, the most common of which are type I and type II (NF1 and NF2). Orthopaedic manifestations are common in NF1, which is also called *von Recklinghausen disease*, whereas they are rare in NF2, which is also called *central neurofibromatosis* or *familial acoustic neuroma*. The clinical findings in NF1 are quite variable, and many of these findings develop over time. Children may exhibit none of the typical findings at birth, but the diagnosis can be made as they grow older and develop the characteristics necessary to confirm a diagnosis of NF1 (48, 57). Although a causative gene for NF1 has been identified, this diagnosis is made by identifying at least two of the clinical findings in Table 8-3.

TABLE 8-3 Neurofibromatosis Type I: Diagnostic Criteria

At least two of the following are necessary for establishing the diagnosis of NF1:

- At least six café-au-lait spots, larger than 5 mm in diameter in children, and larger than 15 mm in adults
- Two neurofibromas, or a single plexiform neurofibroma
- Freckling in the axillae or inguinal region
- An optic glioma
- At least two Lisch nodules (hamartoma of the iris)
- A distinctive osseous lesion, such as vertebral scalloping or cortical thinning
- A first-degree relative with NF1

Cutaneous Markings. Café-au-lait spots are discrete, tan spots (Fig. 8-5). In patients with NF, these spots often appear after 1 year of age, and then they steadily increase in number and size. The spots have a smooth edge, often described as similar to the coast of California, as opposed to the ragged edge of spots associated with fibrous dysplasia, which are described as

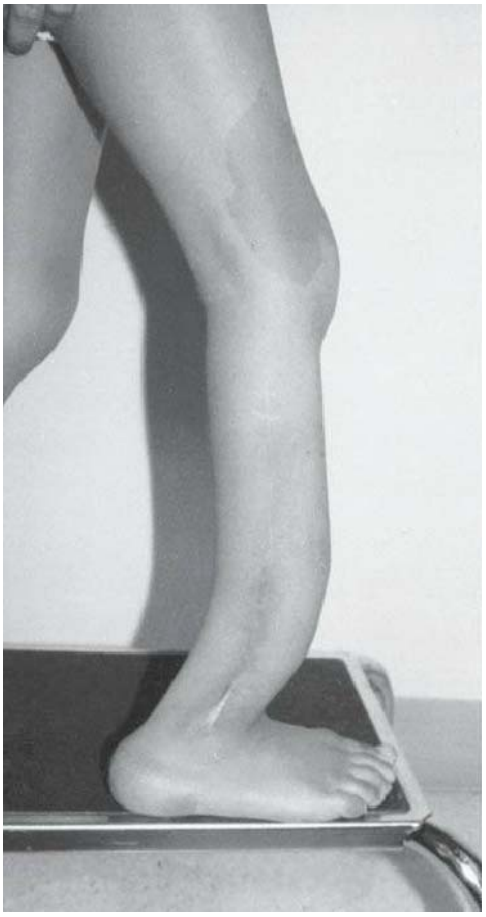


FIGURE 8-5. Neurofibromatosis in a 6-year-old child. Notice the large café-au-lait spot on the thigh and the anterior bowed tibia typical of pseudarthrosis. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

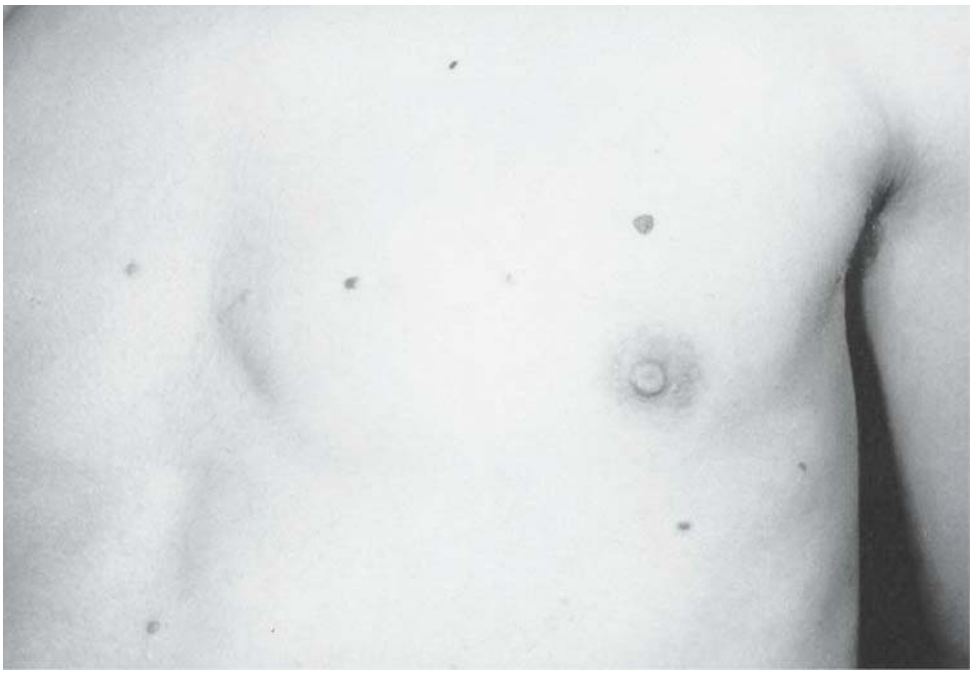


FIGURE 8-6. Neurofibromatosis in a 14-year-old patient. Cutaneous neurofibromas make their appearance with the onset of puberty. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

similar to the coast of Maine. The spots vary greatly in number, shape, and size, and six lesions >1 cm in size are required for the diagnostic criteria. Axillary and inguinal freckling are common and serve as good diagnostic markers, because such freckling is exceptionally rare except in people with NF. Hyperpigmented nevi are dark brown areas that are sensitive to the touch; they typically overlie a deeper plexiform neurofibroma.

Neurofibroma. The two types of neurofibroma are different in their anatomic configuration and clinical morbidity. The most common is the cutaneous neurofibroma, composed of benign Schwann cells and fibrous connective tissue (Fig. 8-6). This type of neurofibroma may occur anywhere, but is usually just below the skin. These neurofibromas may not be detectable until 10 years of age, and with puberty there is a rapid increase in their number. When many are grouped together on the skin, it is known as a *fibroma molluscum*. Plexiform neurofibromas are usually present at birth and are highly infiltrative in the surrounding tissues. The overlying skin is often darkly pigmented. They are highly vascular and lead to limb gigantism, facial disfigurement, and invasion of the neuroaxis (Figs. 8-7 and 8-8).

Osseous Lesions. There are many skeletal manifestations, but the presence of an unusual scoliosis, overgrowth of a part, or a congenital pseudarthrosis lesion seen on radiographs should alert the physician to consider a diagnosis of NF (58). There are a variety of anomalies of bone observed in radiographic images, ranging from a scalloping of the cortex, to cystic lesions in long bones that look much like nonossifying fibromas, to permeative bone destruction (Fig. 8-9). These radiographic findings may mimic benign or malignant bone lesions (49, 50, 59). Radiographs of the pelvis usually show various degrees of coxa valga, and in nearly 20% of patients there is radiographic evidence of protrusio acetabuli (52, 60).

Lisch Nodules. Lisch nodules are hamartomas of the iris. These nodules are present in 50% of all 5-year-olds with NF1, and in all adults with NF1. It is unusual for Lisch nodules to be present in individuals who do not have NF1, so the detection of these nodules can aid in making this diagnosis. However, it may be difficult to detect these lesions, and patients should be sent to an experienced ophthalmologist for this diagnosis. The lesions do not cause any visual disturbances. Once the

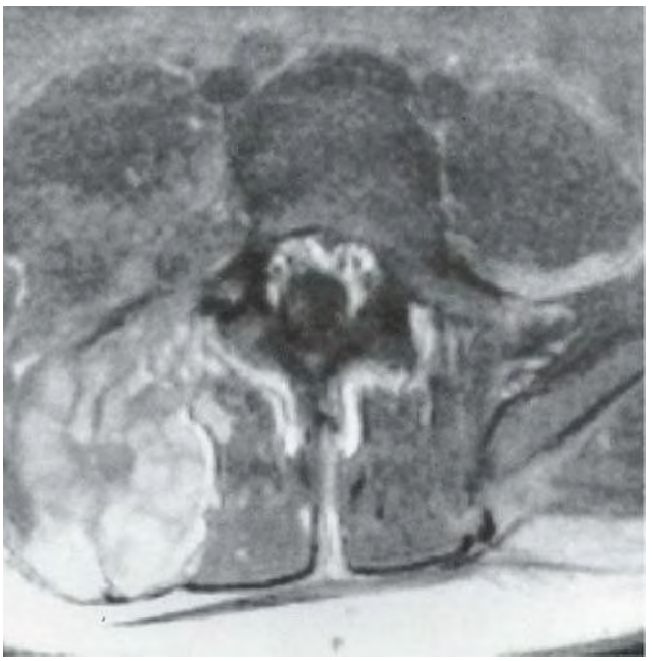


FIGURE 8-7. Neurofibromatosis in a 16-year-old patient. The MRI at the level of L4–L5 demonstrates a large plexiform neurofibroma that invades the neural axis. It extends from the level of L3 to the sacrum.

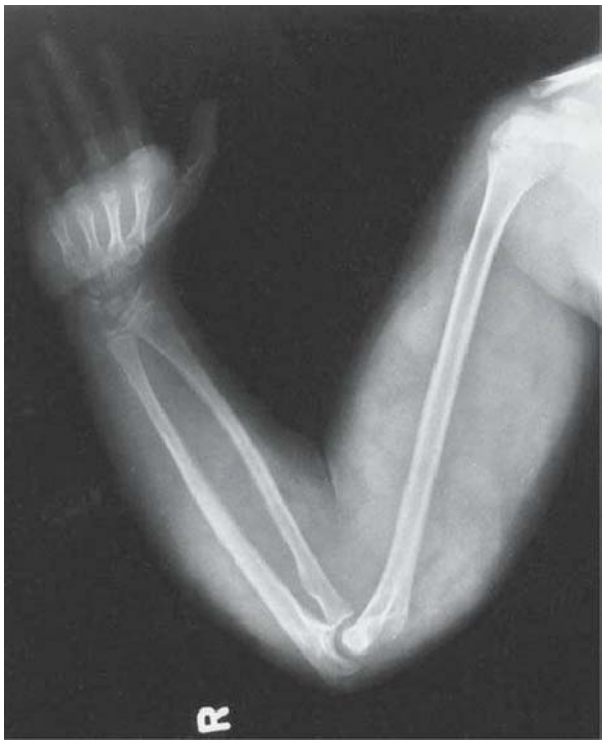


FIGURE 8-8. Neurofibromatosis in a 10-year-old patient. Hypertrophy affects the arm from the shoulder to the fingertips; the major component is soft tissue. Nodular densities throughout the upper arm are consistent with a plexiform neurofibroma. Notice the lack of skeletal overgrowth and some attenuation of the radius and ulna, caused by external compression by the neurofibroma. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

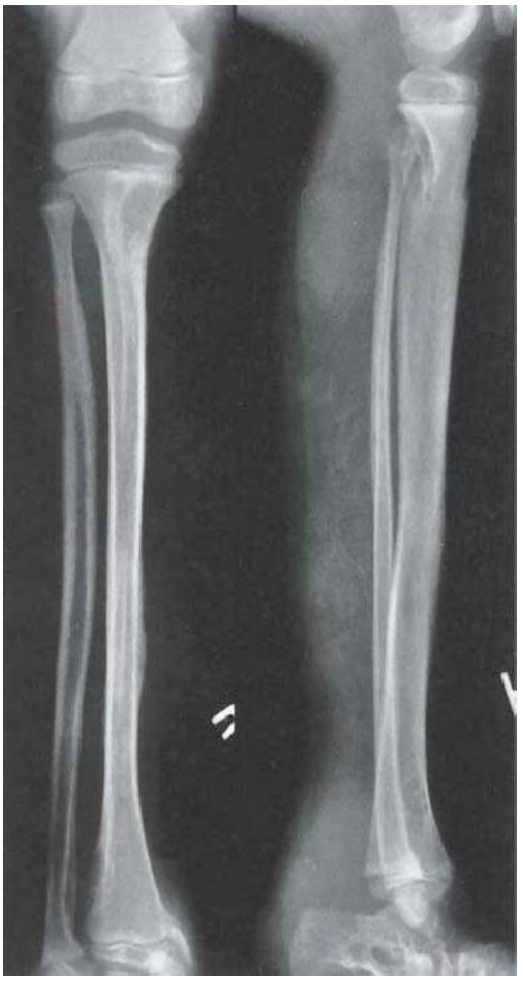


FIGURE 8-9. Neurofibromatosis in a 10-year-old patient. The radiograph shows an array of cystic and scalloped skeletal lesions in the tibia and os calcis of the right leg. Some of the lesions are characteristic of neurofibromatosis. Other lesions, occurring in isolation, can mimic benign fibrous tumors. Scalloped cortical erosion at the upper end of the femur, permeative bone destruction in the region of the os calcis, and metaphyseal cystic lesions are other features. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

diagnosis is established, further ophthalmologic evaluation is not necessary (53, 54).

Etiology. NF is the most common single-gene disorder in humans, affecting 1 in 3000 newborns (61–63). NF1 is an autosomal dominant disorder with 100% penetrance, but one-half of cases are sporadic mutations and are associated with an older-than-average paternal age. The most well-known patient who was presumed to have had NF, Joseph Merrick, also called the *Elephant Man*, probably did not have this condition; his clinical profile better fits Proteus syndrome (64). The *NF1* gene is located on chromosome 17 (65). Its protein product, *neurofibromin*, acts as a tumor suppressor (66). There are also other potential genes located in introns within the *NF1* gene, whose functional significance is unclear.

Neurofibromin plays a role stimulating the conversion of Ras-GTP to Ras-GDP, and as such modulates activation of the Ras signaling system, which is involved in the control of cell growth (67). Mutations in the *NF1* gene cause a disruption in its normal regulatory control of Ras signaling, giving affected cells an abnormal growth pattern. Neurofibromin is expressed at higher levels in the neural crest during development. Cells from the neural crest migrate to become pigmented cells of the skin, parts of the brain, spinal cord, peripheral nerves, and adrenals, thus explaining the common sites of abnormalities in the disorder. Disruption of the normal Ras signaling cascade is probably responsible for the malignant potential of this disorder. Only one of the two copies of the *NF1* gene is mutated in affected patients; however, tumors from such individuals have been found to have only the mutated gene because of loss of the normal copy (68–71). The gene defect also gives a clue to potential novel therapies, because pharmacologic agents that block Ras signaling could be used to treat the disorder. Farnesyl transferase inhibitors block the downstream effects of Ras signaling activation and thus have the potential to be used in the treatment of some of the neoplastic manifestations of NF (72, 73). Another therapeutic approach is the use of statin inhibitors, such as lovastatin, which is thought to regulate Ras signaling by the membrane binding of Ras (52, 53).

Other Types of Neurofibromatosis. Although patients with other forms of NF rarely present to an orthopaedist, one should be aware of these types because musculoskeletal malformations are occasionally present. Patients with NF2 present with acoustic neuromas, central nervous system tumors, and rare peripheral manifestations. There are usually fewer than six café-au-lait spots, and no peripheral neurofibromata. These patients are very unlikely to present with an orthopaedic deformity. There are two much less common types of NF, type 3 and type 4 (NF3 and NF4), in which patients are more likely to develop a problem requiring orthopaedic intervention. Individuals with NF3 present with some of the characteristics of NF1 but also have acoustic neuromas, which are characteristic of NF2. These individuals often have spinal deformity, especially in the cervical region. NF4 presents with the same clinical findings as NF1, except that one of the cardinal features of NF1, namely, Lisch nodules of the iris, is absent (48, 57).

Orthopaedic Manifestations. The orthopaedic manifestations of NF include scoliosis, overgrowth of the limbs, pseudarthrosis, and specific radiographic appearances of bone lesions. Patients with NF often exhibit overgrowth, ranging from a single digit to an entire limb and from mild anisomelia to massive gigantism. As such, the possibility of NF should be considered in a child with focal gigantism, such as macrodactyly. When NF is compared with the more symmetric idiopathic hemihypertrophy, there is disproportional overgrowth involving the skin and the subcutaneous tissue more than the bone (Fig. 8-8)

Scoliosis is common, and curves fall into two categories: a dystrophic curve and an idiopathic curve. Most curves in NF resemble idiopathic scoliosis curves and can be managed like any other idiopathic curve.

The dystrophic scoliotic curve is a short, sharp, single thoracic curve typically involving four to six segments (Fig. 8-10) (60, 74–81). It is associated with deformity of the ribs and vertebrae. The onset is early in childhood, and it is relentlessly progressive. Curves that initially appear to be idiopathic in children under age 7 have almost a 70% chance of becoming dystrophic over time, although there may be subtle clues, for example, mild rib penciling (thinning of the ribs in a shape similar to a pencil point near the vertebrae), suggesting that the curve is actually dystrophic. The most important risk factors for progression are an early age of onset, a high Cobb angle, and an apical vertebra that is severely rotated, scalloped (concave loss of bone), and located in the middle-to-lower thoracic area (78). The combination of curve progression and vertebral malformation mimics congenital scoliosis in appearance and behavior. Dystrophic curves are refractive to brace treatment. Sagittal plane deformities may occur, including an angular kyphosis (i.e., gibbus) and a scoliosis that has so much rotation that curve progression is more obvious on the lateral than on the anteroposterior radiograph (78). In those with angular kyphosis, there is a risk of paraplegia. Dystrophic curves are difficult to stabilize, and it is best to intervene with early surgery involving both anterior and posterior fusion (78, 82–84). Kyphotic deformities are often the most difficult to manage surgically, and strut grafts across the kyphosis anteriorly may be necessary. In rare

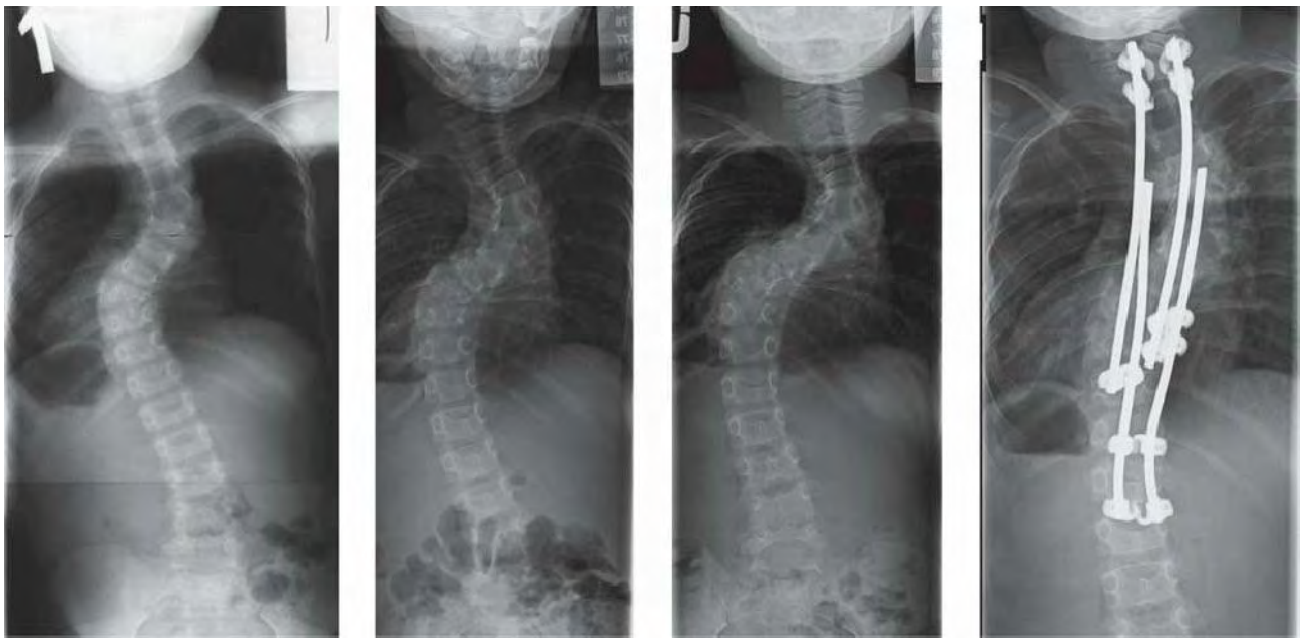


FIGURE 8-10. Neurofibromatosis in a 5-year-old patient. A dystrophic curve is shown in the **left panel**. There is a short-segment scoliosis, with ribboned ribs show cystic irregularities. There was a delay in the recommendation for surgery, and the middle two panels show the rapid progression in the dystrophic curve over the next 12 months. The right panel shows the curve after undergoing surgery including anterior and posterior fusions of the dystrophic segments.

severe cases, the spine can even seem to be "dislocated" because of the kyphosis and scoliosis. In cases with extremely severe deformity, halofemoral or halogravity traction may be necessary to safely straighten the spine to a more acceptable deformity without producing neurologic sequelae. Other reported techniques include inserting a bone graft without instrumentation and then gradually straightening the curve using a cast postoperatively (85). In rare severe cases in which there is a vertebral "dislocation," one can use instrumentation to achieve an overall alignment of the back, while leaving the vertebrae "dislocated" (86). Unusual complications have been reported in the management of such dystrophic curves, such as a rib head migrating into the neural canal resulting in spinal cord compromise (87).

There can be several vertebral abnormalities evident on radiographs. These include scalloping of the posterior body, enlargement of the neural foramina, and defective pedicles, occasionally with a completely dislocated vertebral body (88–92). Such findings may mean that there is a dumbbell-shaped neurofibroma in the spinal canal, extending out through a neural foramina. The dura in NF patients behaves like the dura in patients with a connective tissue disorder, and dural ectasia is common, with pseudomeningoceles protruding through the neural foramina. Unlike neurofibroma, dural ectasia is an outpouching of the dura, without an underlying tumor or overgrowth of spinal elements (Fig. 8-11) (93–96). The incidence of anterolateral meningoceles was underestimated until asymptomatic patients were screened with MRI (58, 97). The erosion of the pedicles may lead to spinal instability, especially in the cervical spine. In rare cases, this can even lead to dislocation of the spine (98, 99). MRI and CT scans are helpful preoperatively in delineating the presence of defective vertebrae or dural abnormalities, and may assist in choosing the levels on which to place instrumentation.

Pseudarthrosis of a long bone is typically associated with NF (76). It usually affects the tibia, with a characteristic anterolateral bow that is obvious in infancy (Fig. 8-12) (100, 101). Fracture usually follows, with spontaneous union being rare and surgical union presenting a challenge. An anterolateral bowed tibia is routinely managed with a total-contact orthosis to prevent fracture, although there are no well-designed studies showing that this is indeed effective. Intramedullary rod fixation seems to offer the best results for the initial management of a pseudarthrosis. Recent studies have shown the importance of achieving neutral tibial alignment in the healing of a tibial pseudarthrosis. The presence of an intact fibula is associated with a lower healing rate, perhaps because of associated tibial malalignment (102). There is a hamartoma of undifferentiated mesenchymal cells at the pseudarthrosis site (75), and in some cases, this is associated with loss of the normal allele of the NF1 gene (76). Neurofibromas have not been identified at the pseudarthrosis site. The pseudarthrosis process may affect the ulna, radius, femur, or clavicle (77, 103–109). In each of these locations, there is a course similar to that in the tibia, with bone loss and difficulty in achieving union (Fig. 8-13). Not all pseudarthroses of the forearm require treatment (110), but if they are symptomatic, the available options include proximal

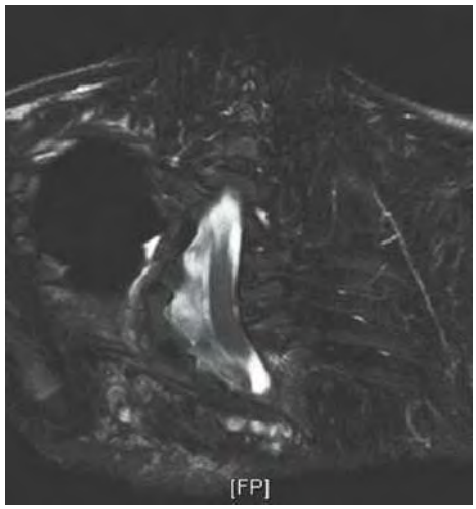


FIGURE 8-11. MRI of the spine of the patient shown in Figure 8-10, showing dural ectasia.

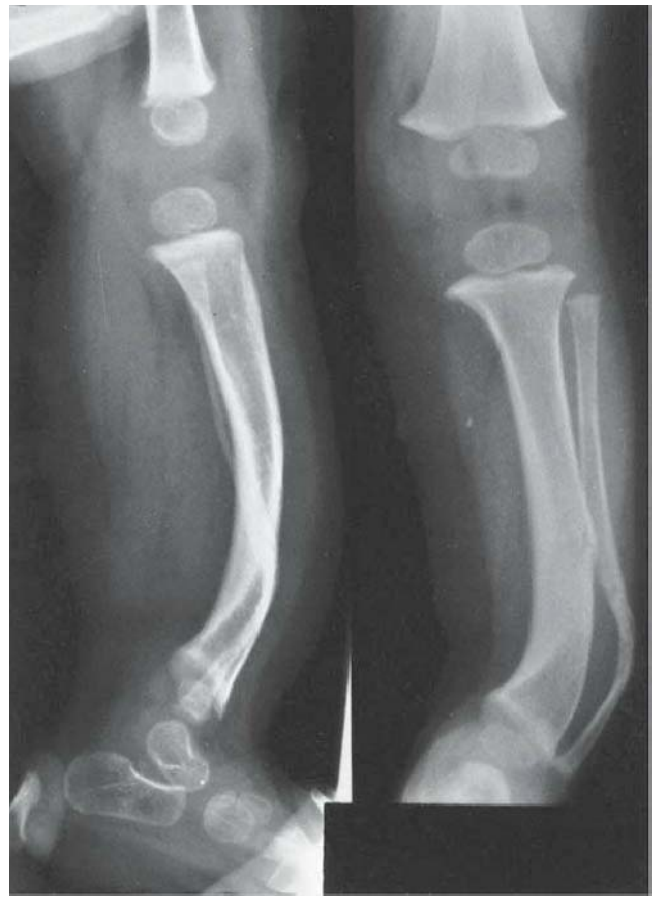


FIGURE 8-12. Neurofibromatosis in a 1-year-old patient. The anterolateral bow of the tibia and the fibula warrant concern about impending fracture and pseudarthrosis. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

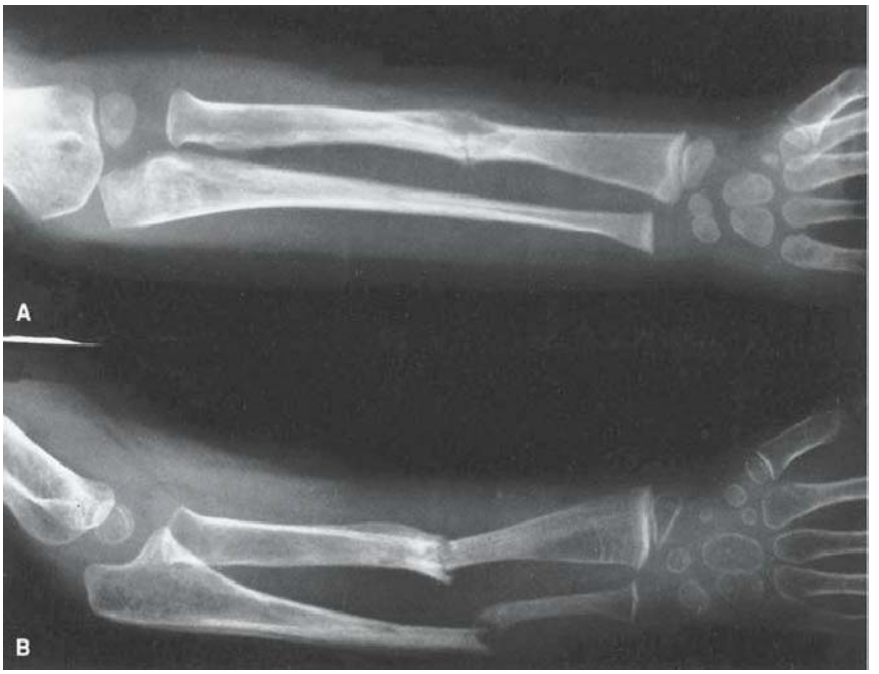


FIGURE 8-13. Neurofibromatosis in a 3-year-old patient. The radiograph shows progressive pseudarthrosis of the radius and ulna after a pathologic fracture. **A:** Fracture through the cystic lesion of the radius and thinning of the midulna. **B:** After 10 months of cast immobilization, pseudarthrosis affects the radius and ulna. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

and distal synostosis to produce a single-bone forearm, the use of a vascularized fibula graft, or resection of the pseudarthrosis with shortening of the forearm and internal fixation (111). Pharmacologic approaches to the pseudarthrosis in NF are reported. A mouse model suggests the use of lovastatin, but the mouse does not develop pseudarthroses, only bowing of the bones, and as such human studies of this approach are needed (53). Direct installation of BMP to the pseudarthrosis site may help in the achievement of union, but variable results are reported, and it is not known if the use of BMP in patients with an inherited premalignant condition has long-term harmful consequences (80).

There are a variety of benign and malignant neoplastic lesions that affect individuals with NF1. Most neurofibromas do not require treatment, but symptomatic lesions may require excision. Plexiform neurofibromas that become symptomatic are very difficult to manage. Their vascularity and infiltrative nature make complete excision almost impossible, with a substantial risk of uncontrollable hemorrhage and neurologic deficit. Although speculative, the use of angiogenesis inhibitors, such as interferon, or experimental agents that modulate the effect of the causative gene mutation, such as farnesyl transferase inhibitors or statin inhibitors, may be beneficial (88, 89).

The incidence of malignancy in NF is reported at rates ranging from under 1% to over 20% (90–92, 112, 113). The most common tumor location is in the central nervous system, with lesions such as optic nerve glioma, acoustic neuroma, and astrocytoma (114). There is a risk of malignant degeneration of a neurofibroma to a neurofibrosarcoma. This process can occur in a central or peripheral neurofibroma (115–118). It can be quite difficult to distinguish a malignant lesion from a benign one. CT scans show areas of low-enhancing density in neurofibrosarcomas (119), but there are no studies confirming the sensitivity and specificity of this finding. Similar patterns can also be visualized using MRI. Routine surveillance for sarcomatous change is impossible because of the large number of neurofibromas. Lesions that increase in size or develop new characteristics should be investigated. There is a propensity for children with neurofibroma to develop other malignancies, such as Wilms tumors or rhabdomyosarcomas.

Hypertension as a result of renal artery stenosis or pheochromocytoma is reported regularly, as is a curious type of metabolic bone disease similar to hypophosphatemic osteomalacia (120, 121). Hypertension is a major risk factor for early death (113). Precocious puberty may occur because of an intracranial lesion (103). Affected children are short, but tend to have large heads. Approximately 50% have an intellectual handicap. Although the mean IQ is low, the range of IQ is quite wide (104). More than the low IQ, it is the difficulty in concentrating (which is common in this condition) that may interfere with the learning process (105). Although it was hoped that lovastatin might help with concentration problems, a recent randomized trial suggests that this is not the case (106).

Beckwith-Wiedemann Syndrome. Beckwith-Wiedemann syndrome is a triad of organomegaly, omphalocele, and a large tongue (107). The incidence is 1 in 14,000, and it is probably an autosomal dominant trait of variable expression. Patients are large, although this feature is not always noticed at birth (108). The child is in the 97th percentile for size by 1 year of age. The tongue is gigantic at birth, and although it tends to regress, hemiglossectomy is sometimes needed. Omphalocele is common, and 15% of the babies born with omphaloceles have Beckwith-Wiedemann syndrome. The abdominal viscera are enlarged, and a single-cell hypertrophy

accounts for the large organs: in the adrenals, giant cortical cells; in the gonads, an increased number of interstitial cells; and in the pancreas, islet cell hyperplasia. This underlies the 10% risk of developing benign or malignant tumors. Wilms tumor is the most common.

Beckwith-Wiedemann syndrome is linked to chromosome 11p15, which is near the Wilms tumor gene (11p13) and the insulin-like growth factor gene (11p15.5) (109). There may be some paternal genomic imprinting (122, 123). The closeness of the Beckwith-Wiedemann gene locus and these embryonal tumor gene loci accounts for the dysregulation of the tumor-related genes and the associated overgrowth and higher incidence of tumors seen in this syndrome.

Pancreatic islet cell hyperplasia causes hypoglycemia. It is crucial that the neonatologist diagnose this syndrome early so as to prevent the consequences of hypoglycemia. If it is not managed properly, seizures occur at day 2 or 3. Central nervous system damage from the hypoglycemia leads to a cerebral palsy–like picture. The cerebral palsy–like findings confuse the diagnosis of this syndrome and make the management of these patients more complex. The diagnosis can occasionally be made prenatally by ultrasound (124, 125).

The clinical feature that makes the orthopaedist suspect the presence of this disorder is the unusual combination of two otherwise common problems: spastic cerebral palsy and hemihypertrophy (Fig. 8-14). The spasticity is thought to be a result of the neonatal hypoglycemic episodes, especially if accompanied by neonatal seizures, but spastic hemiplegia is most commonly seen. In general, children with cerebral palsy tend to be small; Beckwith-Wiedemann syndrome should be suspected if a large child has spastic cerebral palsy. Asymmetric growth affects about 20% of the patients. It is usually true hemihypertrophy, but it can be significant if the spastic hemiplegia affects the smaller side.

Children with Beckwith-Wiedemann syndrome are predisposed to a variety of neoplasms, most notably Wilms tumor. Abdominal ultrasounds at regular intervals until the age of 6, to screen for Wilms tumor, are advocated. A series comparing a screened population (ultrasounds every 4 months) with a population that was not screened showed that none of the children in the screened group presented with late-stage Wilms tumor, whereas one-half of the children who developed Wilms tumor in the nonscreened group presented with late-stage disease. This study suggests that screening every 4 months will identify early disease. However, a larger study is needed to determine whether screening improves patient survival (125, 126). Other tumors types, such as alveolar rhabdomyosarcoma, can present in a new born (100).

Scoliosis is common and usually behaves like an idiopathic spinal deformity, but there may be insignificant morphogenic variations, such as 13 ribs. It is managed in the same way as any idiopathic curve. Other orthopaedic findings include cavus feet, dislocated radial heads, and occasional cases of polydactyly (127, 128). All of these can be managed the same as in sporadic deformities.

FIGURE 8-14. Beckwith-Wiedemann syndrome in an 8-year-old patient. Hemihypertrophy on the right, a part of this syndrome, is combined with hemiatrophy on the left, caused by acquired encephalopathy secondary to hypoglycemic seizures as a newborn, leading to a significant leg-length discrepancy of 4.6 cm. Abdominal scars are a consequence of omphalocele repair. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

Russell-Silver Syndrome. The patient with Russell-Silver syndrome is defined clinically as a short child with body asymmetry and a characteristic facial shape (129–131) (Fig. 8-15). The diagnostic characteristics include (i) a birth weight ≤ 2 standard deviations below the mean, (ii) poor postnatal growth ≤ 2 standard deviations from the mean at diagnosis, (iii) preservation of occipitofrontal head circumference, (iv) classic facial features, and (v) asymmetric growth (132). Poor feeding is also a common occurrence. The cause of the disorder is unclear; although some cases are associated with uniparental disomy, there is a suggestion of autosomal dominant inheritance, and there is some evidence implicating an abnormal intrauterine environment (130, 131). The associated genitourinary malformations and the variation in the pattern of sexual maturation chemically (increased gonadotropin secretion) or clinically (precocious sexual development) suggest that hypothalamic or other endocrine disturbances may contribute to the pathogenesis. Affected children are small at birth and remain below the 3rd percentile throughout growth, with a marked delay in skeletal maturation. Body asymmetry with hemihypertrophy affects 80% of them. The asymmetry

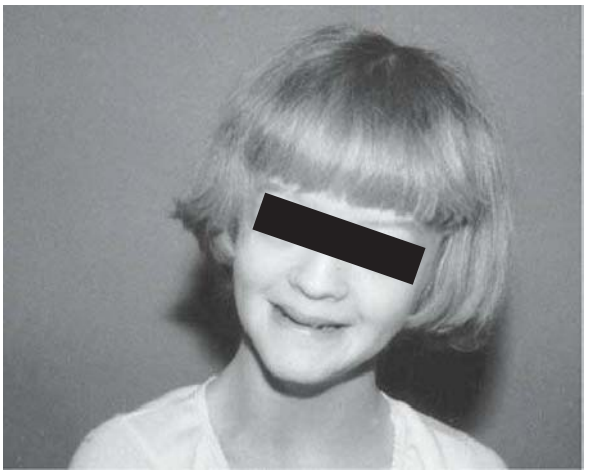


FIGURE 8-15. Russell-Silver syndrome. The triangular face is seemingly small for the size of the skull.

averages approximately 2 cm at maturity, but can be as much as 6 cm. Regardless of the magnitude of the discrepancy, it is clinically more apparent because the child is small. The face is characteristically triangular and seemingly too small for the cranial vault. There have been several reports of variations in sexual maturation pattern and malformations of the genitourinary system.

Radiologic analysis discloses a remarkable array of orthopaedic findings, but it is not clear which form part of the syndrome and which are coincidental (133–137). Scoliosis is usually idiopathic. Hand and foot abnormalities include clinodactyly, polydactyly, and hallux varus. Developmental hip dysplasia, avascular necrosis of the femoral head, and slipped capital femoral epiphysis (SCFE) may be present. Many radiographic changes, such as the minor hand abnormalities, suggest a disturbed morphogenesis.

Treatment consists of managing leg-length equality. This can be difficult because individual growth curves may vary, the skeletal age is very retarded, and puberty may be very abnormal. It is easy to miss the appropriate timing for epiphysiodesis. Growth hormone has been administered in an attempt to improve stature. Although the use of growth hormone will increase growth velocity, it is not yet known whether the ultimate height is increased (138).

Cytogenetic studies found anomalies on chromosomes 1, 7, and 17, but most patients have anomalies involving chromosome 7. However, no single causative gene has yet been identified. It is not known whether screening for Wilms tumor, as is performed in other forms of hemihypertrophy, is necessary. Despite early evidence that the insulinlike growth factor receptor, which plays a causative role in Wilms tumor, is involved in this syndrome, more comprehensive molecular genetic investigations have not found any abnormalities in this gene. However, there is a case report of Wilms tumor developing in an affected patient (139), leading some to recommend screening for Wilms tumor in these patients as one would in any other hemihypertrophy.

Proteus Syndrome. Proteus syndrome is an overgrowth condition in which there is a bizarre array of abnormalities that include hemihypertrophy, macrodactyly, and partial gigantism of the hands or feet, or both. The key to this diagnosis is worsening of existing symptoms and the appearance of new ones over time. There is a characteristic appearance to the plantar surface of the feet, often described as similar to the surface of the brain. Unlike in other overgrowth syndromes, an increased incidence of malignancy has not been reported in Proteus syndrome (140–144).

The cause of this syndrome is not known. Although there are case reports of familial occurrence, the vast majority of cases are sporadic (145–147). It is most likely due to a gene that is mutated in a mosaic manner (mutated in the affected tissues but not in the normal tissues), similar to McCune-Albright syndrome (polyostotic fibrous dysplasia). Such a mutation can occur very early in development in a single cell, which will divide to ultimately form various structures throughout the body.

The Proteus syndrome is named after the ancient Greek demigod who could change appearance and assume different shapes. The progressive nature of the deformities seen in this syndrome can lead to grotesque overgrowth, facial disfigurement, angular malformation, and severe scoliosis (148). Joseph Merrick, called the *Elephant Man*, is now believed to have had this syndrome rather than NF (149).

The signs of Proteus syndrome overlap other hamartomatous overgrowth conditions, such as idiopathic hemihypertrophy, Klippel-Trenaunay syndrome, Maffucci syndrome, and NF. However, unlike these other syndromes, the features here are more grotesque and involve multiple tissue types and sites. Proteus can be differentiated from NF1 by the lack of café-au-lait spots and Lisch nodules (150). A rating scale, which assigns points on the basis of clinical findings (macrodactyly, hemihypertrophy, thickening of the skin, lipomas, subcutaneous tumors, verrucae, epidermal nevus, and macrocephaly), may be used to assist in diagnosis (151). However, the finding of worsening overgrowth features over time is usually sufficient to make this diagnosis.

Most children who present with macrodactyly do not have it as part of Proteus syndrome. In these sporadic cases, an isolated digit is involved or, when multiple digits are involved, these are located adjacent to each other. Macrodactyly affecting nonadjacent toes or fingers or opposite extremities is almost always due to Proteus syndrome. There is a characteristic thickening and deep furrowing of the skin on the palms of the hands and soles of the feet. The array of cutaneous manifestations includes hemangiomas and pigmented nevi of various intensities, and subcutaneous lipomas (Fig. 8-16). Varicosities are present, although true arteriovenous malformations are rare. There are cranial hyperostoses and occasionally exostosis of the hands and feet.

Macrodactyly seems to correspond to overgrowth along the terminal branches of a peripheral sensory nerve. Digital involvement in the hand favors the sensory distribution of the median nerve (1). The index is the most frequently affected

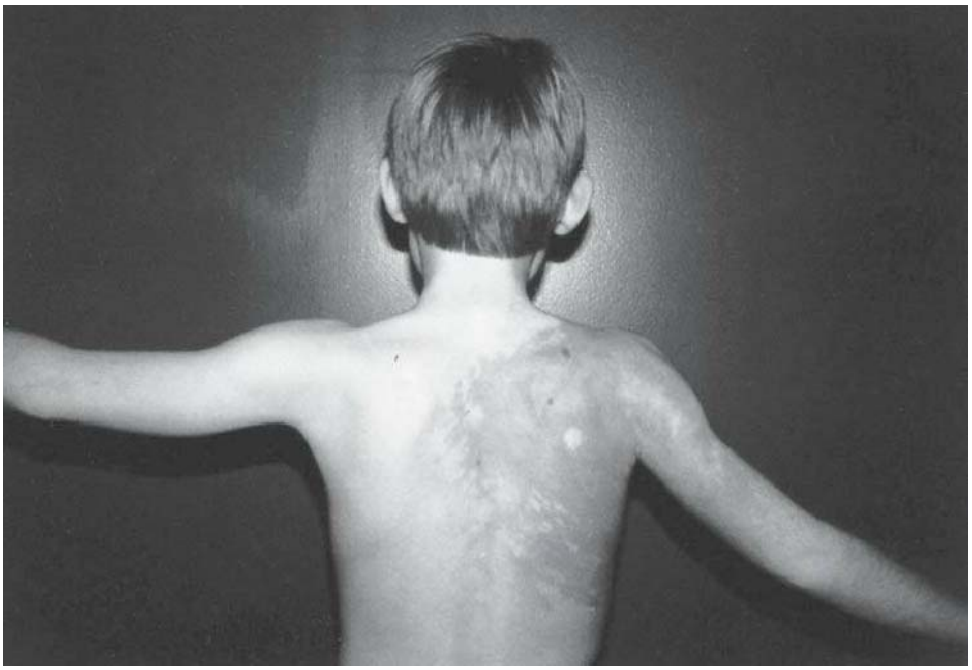


FIGURE 8-16. Proteus syndrome. Notice the cutaneous markings, large hemangioma of the shoulder, and lightly pigmented area on the back. There is some atrophy of the shoulder and arm muscles and a fixed contracture of the elbow.

finger, followed by the long finger and the thumb. It is the second toe that is most commonly macrodactylous. The regional sensory nerve is greatly increased in size, taking a tortuous route through the fatty tissue.

There is a wide range of orthopaedic deformities, including focal and regional gigantism, scoliosis, and kyphosis (152, 153). Rather large vertebral bodies, known as *megaspondylodysplasia*, are present (154). Angular malformations of the lower extremities, especially genu valgum, are common. Because the genu valgum is often associated with restricted range of motion, flexion contractures, and pain in the joints, it is postulated that an intra-articular growth disturbance contributes to the angular malformation. Hip abnormalities that show up in roentgenographic tests, acetabular dysplasia for example, are frequently discovered in asymptomatic patients. Deformities in the hindfoot are frequent and are usually heel valgus, but congenital equinovarus and "Z-foot" deformities have also been described (150, 153, 155).

Recurrences after various surgical intervention are very common. This is probably due to an underlying growth advantage in affected tissues that cannot be corrected operatively. Thus, musculoskeletal deformities caused by Proteus syndrome can be very difficult to manage. When the foot becomes difficult to fit into a shoe because of macrodactyly, it is best managed by ablation rather than debulking (156). Anisomelia is best managed with epiphysiodesis. Osteotomies can correct angular malformations, but the decision to undertake surgical correction must take into account the possibility of a rapid recurrence of the deformity after corrective surgery (152, 153). The use of growth modulation (e.g., 8-plate) to manage limb angular deformity is a rather promising approach (120), but publications on the results of this approach are lacking. In some cases, a sudden overgrowth of the operative limb has been reported. There are anecdotal reports of soft-tissue procedures to "debulk" overgrown lesions; however, there are no series in the literature reporting results of these procedures, and our experience with them is that the results are only temporary. In rare cases, nerve or spinal cord impingement can occur. Nerve compression can be managed using decompression, but spinal cord compression is difficult, if not impossible, to successfully treat operatively (157, 158). Scoliosis can occur and seems to be caused by overgrowth of one side of the spine (159). Since mixed results are obtained from surgical treatment in this disorder, operative treatment should be reserved for individuals who have exhausted nonsurgical management. Sometimes, the operative procedures can be used as a temporizing measure, and patients may need to have repeat procedures performed throughout life.

Functional ability depends on the severity of the limb deformity and the presence of intracranial abnormalities (143, 160). The life expectancy is unknown, but many adult patients have been reported. Intubations can be difficult because of overgrowth of structures surrounding the trachea.

DEVELOPMENTALLY IMPORTANT SIGNALING PATHWAYS

During embryonic development, cell signaling systems are activated in a coordinated manner to cause cells to proliferate, move, and undergo programmed cell death, so as to allow the organism to pattern normally and develop into an adult. Normal patterning is altered by mutations in the genes that encode proteins that play roles in these pathways. Environmental events such as exposure to a teratogen can also dysregulate these same pathways, resulting in a phenotype similar to that of a gene mutation. Such events occurring in a pathway that is important for skeletal development can result

in a musculoskeletal malformation. These disorders can be identified at birth, because the problem is present at the start of development. Despite this, sometimes, the abnormalities do not become obvious to parents or physicians until the child is older. Because these are generally patterning problems, surgery to correct malalignment is usually quite successful. There are frequently manifestations in other organ systems, because the same developmental signaling pathways play important roles in the development of multiple organs. These disorders are not associated with an increased rate of neoplasia. Symptoms from the malformations often increase with age because the abnormally shaped structures cannot sustain the stresses of normal activity. This results in the early development of degenerative problems. These disorders are usually inherited in an autosomal dominant manner, although the inheritance pattern is more variable than in disorders caused by genes encoding for structural proteins or for proteins implicated in neoplasia.

Nail-Patella Syndrome. Children with nail-patella syndrome have a quartet of findings that include nail dysplasia, patellar hypoplasia, elbow dysplasia, and iliac horns (161). The most prominent feature is dystrophic nails (Fig. 8-17A). The nail may be completely absent, hypoplastic, or have grooves and distortions in its surface (162). The thumb is more involved than the small finger, and the ulnar border more involved than the radial. The hands are often very symmetric, and fingernails are more involved than toenails.

The second cardinal feature is hypoplastic patellae (163). They are quite small, or may be entirely absent (Fig. 8-17B). Where present, they are unstable, and may be found in a position of fixed dislocation. The patellar abnormality highlights the total knee dysplasia, with an abnormal femoral condyle and a peculiar septum running from the patella to the intercondylar groove (septum interarticularis), dividing the knee into two compartments. Abnormalities in varus and valgus alignment occur, with valgus more common because of the small, flat lateral femoral condyle (163).

A third feature is a dislocated radial head (163, 164) (Fig. 8-17C). The elbow joint is dysplastic, with abnormalities in the lateral humeral condyle, in many ways mimicking the dysplasia of the knee. The trochlea is large and the capitellum is hypoplastic, creating an asymmetric shape that may predispose the radial head to dislocation.

The fourth and pathognomonic feature is iliac horns: bony exostoses on the posterior surface of the ilium (165) (Fig. 8-17D). They usually cannot be found on physical examination, are asymptomatic, and require no treatment.

Nail-patella syndrome is caused by a mutation in the *LMX1B* gene. This gene is a homeodomain protein, which plays a role regulating transcription in limb patterning during fetal development. Mutation in the gene will disrupt normal limb patterning and alter kidney formation, resulting in deformities in the extremities and an associated nephropathy (166).

Children with the syndrome have short stature, the height being between the 3rd and 10th percentiles. There may be a shoulder girdle dysplasia, and a variety of abnormalities of the glenoid and the humeral head are possible. These, however, merely represent curious radiographic features and not any significant functional disability (167). There is a foot deformity that is sometimes the chief presenting complaint of children with nail-patella syndrome (163, 168). The foot deformities include variations of stiff calcaneal valgus, metatarsus adductus, and clubfeet.

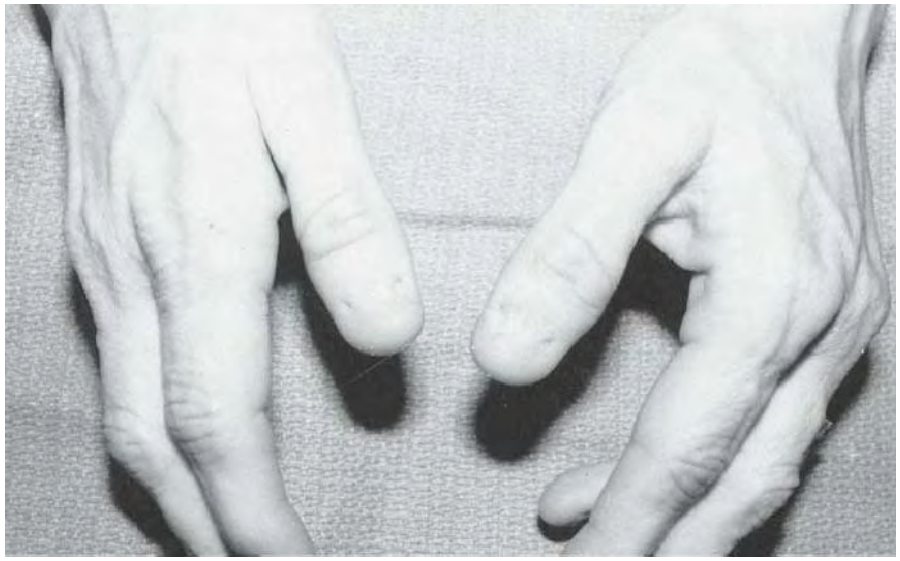
There is a restricted range of motion, and contractures affect several large joints; these include knee-flexion deformities and external rotation contracture of the hip. When these contractures are severe and accompanied by stiff clubfeet, the condition may be misdiagnosed as arthrogryposis multiplex congenita. Madelung deformity, spondylolysis, and in some adults, inflammatory arthropathy may be present (161, 169, 170).

Knee disability is variable and related to the magnitude of quadriceps dysfunction and the dislocated patella. At long-term follow-up, knee pain is the main musculoskeletal complaint in patients with nail-patella syndrome (171). Small femoral condyles make it difficult to achieve patellar stability. As a rule, limited soft-tissue or capsular releases are ineffective, but combined proximal and distal patella realignments have an overall favorable outcome (163, 172). A contracted and fibrotic quadriceps may result in a knee extension contracture, and in such cases quadricepsplasty is indicated along with the patella realignment. More commonly, an associated knee-flexion deformity may require hamstring release and posterior capsulotomy, although results have been inconsistent (163). Residual deformity, which is usually related to flexion or rotation, is managed by femoral osteotomy toward the end of the first decade of life. Osteochondritis dissecans of the femoral condyle is relatively common (Fig. 8-17B). An intra-articular septum makes arthroscopic management difficult, but the septum can be removed arthroscopically.

The radial head dislocation is asymptomatic in young children, but may become symptomatic with time. In symptomatic individuals, excision of the radial head will improve symptoms arising from the prominent lateral bump, but the range of motion is rarely improved. Although traditional teaching advocates performing radial head excision after skeletal maturity, earlier excision in symptomatic children does not seem to be associated with significant problems (163). Dislocated hips (173) and clubfeet can occur, and can be managed using techniques similar to those in idiopathic cases.

The most important nonorthopaedic condition is kidney failure. The nephropathy of nail-patella syndrome causes significant morbidity, affecting the patient's longevity. There is great variability in the age at onset and severity of the nephropathy (174). All patients should be referred for a nephrology evaluation when this diagnosis is made. Patients may go on to chronic renal failure, requiring long-term nephrology management.

Goldenhar Syndrome. The association of anomalies in the eye, ear, and vertebrae are termed *ocular–auricular–vertebral dysplasia* or *Goldenhar syndrome* (175). There is variability in the



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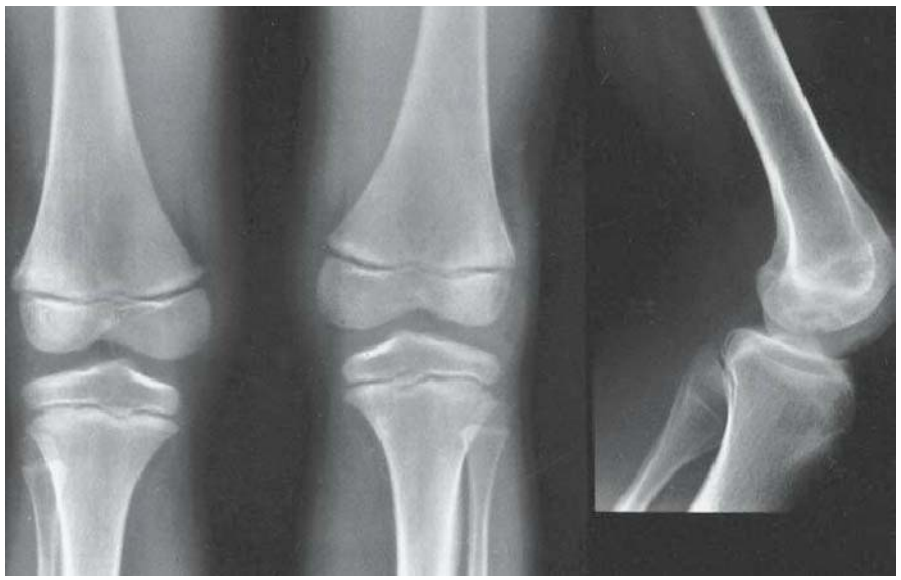

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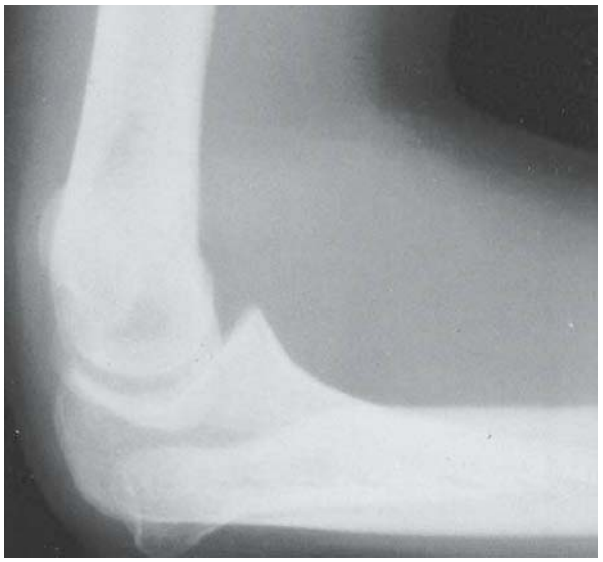

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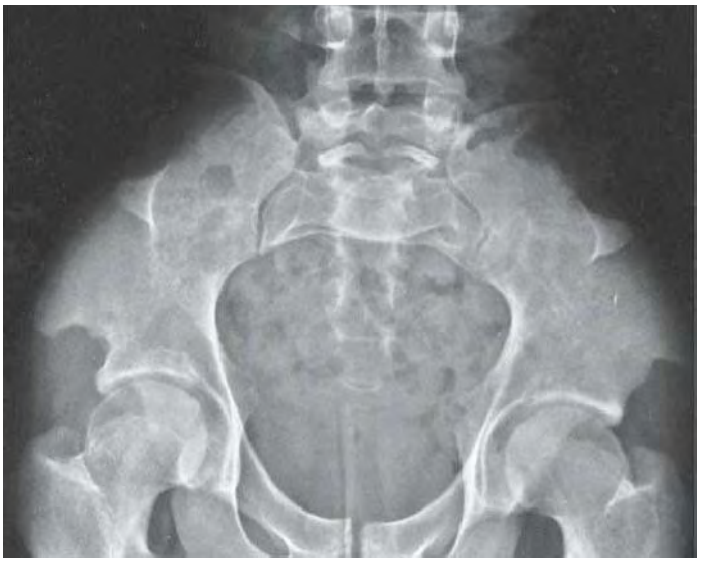


D

FIGURE 8-17. Nail-patella syndrome. The classic quartet of features consists of dystrophic nails **(A)**, absent patellae (notice the region of osteochondritis dissecans on the lateral film) **(B)**, posterior dislocation of the radial head **(C)**, and iliac horns **(D)**.

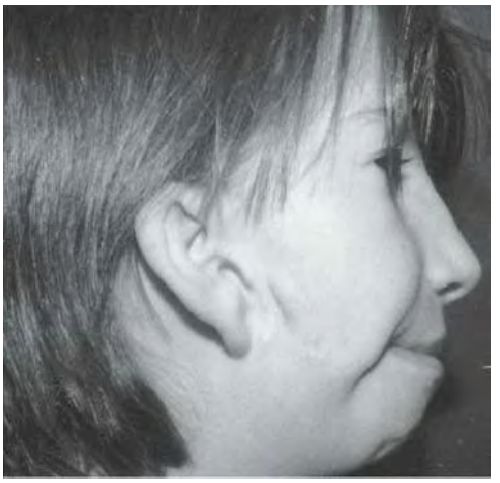
severity of the anomalies and they are frequently associated with other malformations (176, 177). It has an estimated incidence of 1 in 5600 births (178), and roughly 2% of individuals with congenital spinal abnormalities will have another manifestations of ocular–auricular–vertebral dysplasia (138).

The typical eye defect is an epibulbar dermoid on the conjunctiva (Fig. 8-18A). Preauricular fleshy skin tags are found in front of the ear, and pits extend from the tragus to the corner of the mouth (Fig. 8-18B). In some patients, the ear may be hypoplastic or absent. The eye and ear anomalies are unilateral in 85% of these children, and facial asymmetry is the result of a hypoplastic mandibular ramus, invariably on the same side as the ear anomalies (Fig. 8-18C).

Vertebral anomalies may occur anywhere along the spine, although the lower cervical and the upper thoracic locations predominate (Fig. 8-18C). Hemivertebrae are the most common defect, with an occasional block fusion. Neural tube defect occurs more often than in the general population, and it may involve any portion of the spine, or even the skull (an encephalocele). Half of the patients have clinically detectable scoliosis (179).

The congenital curve can cause cosmetic concerns, but these need to be considered in the context of the other abnormalities, which may outweigh the cosmetic implications of the spinal deformity. In addition, Sprengel deformity and rib anomalies may be present in association with the congenital curves in the cervical–thoracic region, and these contribute to the cosmetic implications of the condition. The congenital curves should be managed like congenital scoliosis of other etiologies, although management based on cosmetic concerns needs to be made in the context of the other deformities. Early surgery should be considered when there is progression of the congenital curve. Preoperative CT scan and MRI are recommended to delineate the anatomy of the congenital curve and determine whether there is any intraspinal pathology or occult posterior element defects.


A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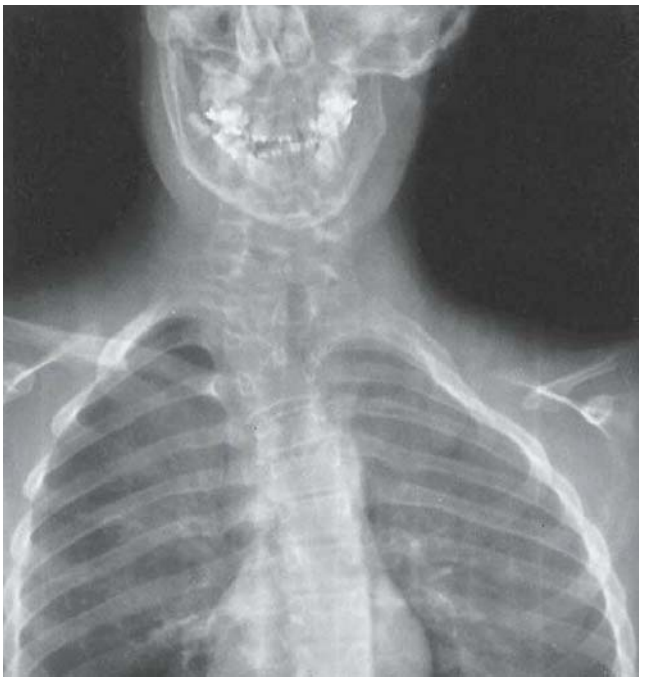
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FIGURE 8-18. Goldenhar syndrome. **A:** Facial asymmetry and epibulbar dermoid of the right eye. **B:** Malformed ears with preauricular tags and sinuses. **C:** X-ray film demonstrates the congenital anomalies of the lower cervical and the upper thoracic spine. Hypoplasia of the ascending ramus of the mandible accounts for the facial asymmetry. The clavicle is absent on the same side as the deformation of the face. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

There is frequently a compensatory curve below the congenital curve that can behave like idiopathic scoliosis. The compensatory curve can cause as much, if not more of a problem for the patient as the congenital curve. This curve is managed the same as idiopathic scoliosis. Brace treatment has no effect on the congenital curve, and although orthotic management has been used for the compensatory curve, its success rate seems lower than for idiopathic scoliosis although high-quality comparative studies of its efficacy are lacking.

Intubation for anesthesia may be difficult because of the small jaw, stiff neck, and upper airway dysmorphology (180). Other anomalies include congenital heart disease (e.g., ventricular septal defect) (176), cleft lip, and cleft palate (181). Mental retardation, reported to affect between 10% and 39% of patients, is more common in cases involving microphthalmia or an encephalocele (143, 182).

Cornelia de Lange Syndrome. Cornelia de Lange syndrome is associated with a characteristic face, and growth retardation, which makes the clinical diagnosis of Cornelia de Lange syndrome reasonably reliable (183). The face has immediately recognizable downturned corners of the mouth, eyebrows meeting in the midline (synophrys), elongated philtrum, and long eyelashes (184, 185) (Fig. 8-19).

Mutations in a number of genes, which all regulate the same signaling pathway, are identified in Cornelia de Lange syndrome. About half of affected individuals have a mutation in the *N1PBL* gene, which encodes a protein that is a component of a multiprotein complex, called the *cohesin complex*. The mutation alters the activity of a developmentally important signaling pathway called *Notch* (186, 187). Notch plays a major role in central nervous system development, hence the associated mental retardation. An X-linked form of the disorder can be caused by mutation in the SMC1L1 gene, which also encodes a component of the cohesin complex. A mild variant of Cornelia de Lange syndrome is related to mutation in the SMC3 gene, which encodes yet another component of the cohesin complex. Duplication or deletion of the chromosome band 3q25-29 produces a phenotype similar to Cornelia de Lange syndrome (188, 189). In these instances, the mother is always the transmitting parent, suggesting genomic imprinting. The syndrome is relatively common, occurring in 1 in 10,000 live births, and it is possible to make a prenatal diagnosis by ultrasound (135, 136, 190, 191).

Most have mild orthopaedic deformities of the upper extremities (191–197) (Fig. 8-20). They form a curious constellation of a small hand, a proximally placed thumb, clinodactyly of the small finger, and decreased elbow motion, usually caused by a dislocated radial head. This combination rarely causes any disability. Some patients, however, have severe deformities of the upper extremity in the form of an absent ulna and a monodigital hand, a condition that can be unilateral or bilateral (Fig. 8-20).

The lower extremities are less often affected. Tight heel cords and other cerebral palsy–like contractures can be seen. These can be managed similarly to cerebral palsy, but there seems to be a higher rate of recurrence (198). Syndactyly of the toes is fairly constant. Aplasia of the tibia has been reported rarely. There is possibly a higher incidence of Legg-Perthes disease, approaching about 10%. Scoliosis can occur and should be managed similarly to scoliosis in cerebral palsy. Most of the skeletal deformities in Cornelia de Lange syndrome are asymptomatic and probably do not benefit from surgical intervention (198).

The small size begins with intrauterine growth retardation. Children remain small, with a delayed skeletal age. The mortality rate in the first year of life is high because of defective swallowing mechanisms (199), gastroesophageal reflux (200), aspiration, and respiratory infections. If the children survive their first year, they usually do well, but the long-term outcome is unclear.

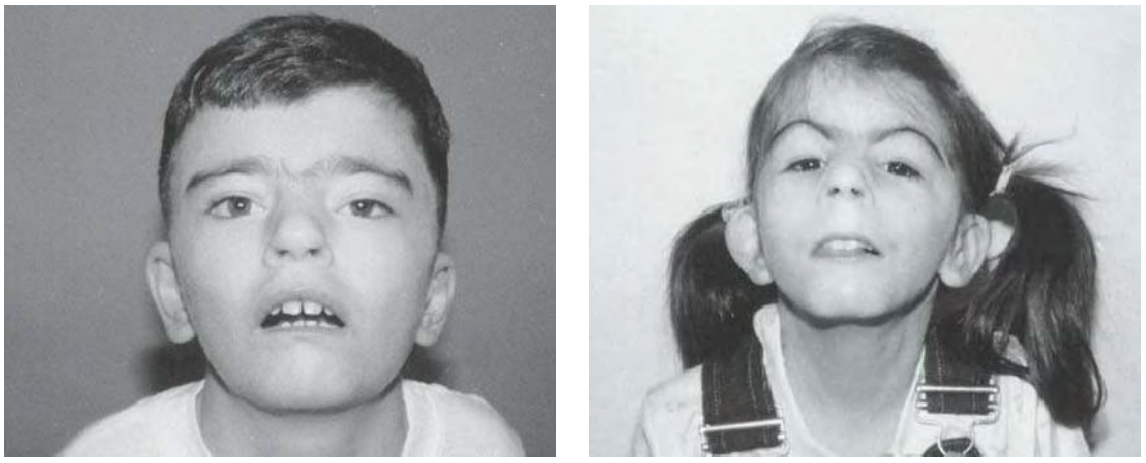


FIGURE 8-19. Cornelia de Lange syndrome. Notice the classic facial features of heavy eyebrows meeting in the midline, upturned nose, downturned corners of the mouth, and long eyelashes in a 13-year-old boy **(A)** and a 7-year-old girl **(B)**. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

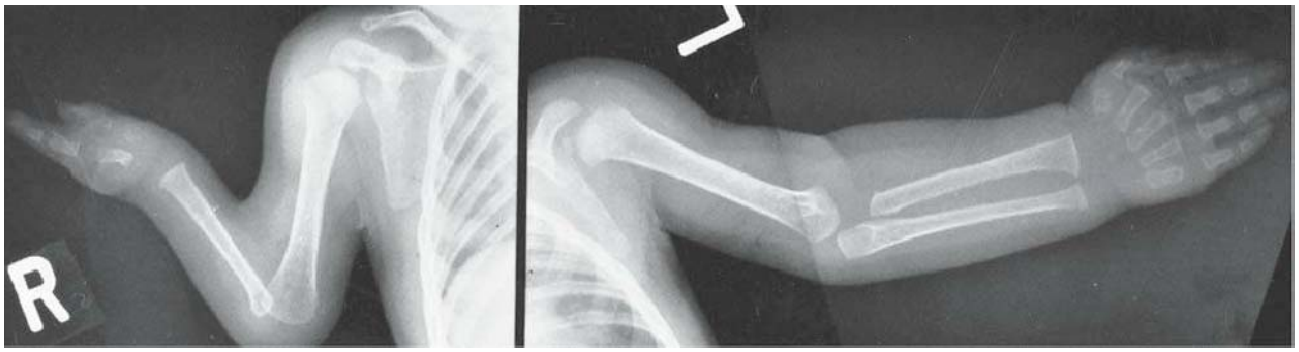


FIGURE 8-20. Cornelia de Lange syndrome: a child with a severely affected upper extremity on her right side (i.e., absent ulna and fingers) and a mildly affected arm on her left (i.e., short thumb and dysplasia of proximal radius). (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

Almost all of them walk, but their milestones are delayed. There is retarded mentation, but the added features of no speech and no interactions cause major disability (201). Self-mutilating behavior can be an obstacle to orthopaedic care (202, 203).

Orthopaedic interventions need to be considered in the overall functional context of the individual. Braces, physical therapy, and surgery for tight heel cords, using similar indications as in cerebral palsy are justifiable. Upper extremity surgery is not indicated unless improved performance capacity is ensured. Patients with Cornelia de Lange syndrome rarely if ever use upper extremity prostheses. Lower extremity prostheses, however, should be prescribed for the rare case with tibial deficiency. Because the gastroesophageal reflux and swallowing disorders may persist well past the first year, there is a higher risk of anesthesia complications (204).

FETAL ENVIRONMENT

Syndromes caused by problems in the fetal environment can share similarities with conditions caused by genes that encode proteins that are important in normal development. Many teratogenic agents modulate the same pathways that are dysregulated by the mutations that cause such syndromes. A good example of this is holoprosencephaly, a midbrain patterning disorder. This can be caused by mutations in a gene called *sonic hedgehog*, and can also be caused by teratogenic agents that block the hedgehog signaling pathway, such as derivatives found in the plant *Veraculum californium* (205, 206).

Fetal Alcohol Syndrome. Fetal alcohol syndrome is a pattern of malformations found in children of alcoholic mothers. There is a great deal of variability in the findings associated with fetal alcohol exposure and the full-blown syndrome is usually seen only in children of chronic alcoholics who drink throughout pregnancy. Multiple terms are used to describe the effects that result from prenatal exposure to alcohol, including fetal alcohol effects, alcohol-related birth defects, alcohol-related neurodevelopment disorder, and, most recently, fetal alcohol spectrum disorder (207). Although the risk to alcoholic mothers is known, there is substantial difference of opinion about the effects of moderate alcohol use during pregnancy (208–210). This is in part because fetal exposure to alcohol may be relatively common. Indeed, it is estimated that about 12% of U.S. women who are sexually active, do not use contraception effectively, and drink alcohol frequently or binge drink, thereby putting them at risk for an alcohol-exposed pregnancy. As such, alcohol is the most likely teratogen for a mother to encounter (211). Because no safe threshold of alcohol use during pregnancy has been established, the Centers for Disease Control recommend that women who are pregnant, planning a pregnancy, or at risk for pregnancy should not drink alcohol. The overall incidence of full-blown fetal alcohol syndrome is reported to be between 0.5 and 2.0 per 1000 live births (212, 213), making this condition as common as Down syndrome. For an alcoholic mother, there is a 30% risk for fetal alcohol syndrome in her child.

A cardinal clinical feature is disturbed growth; the children have intrauterine growth retardation, small weight, and small length at birth, and these limitations remain despite good nutrition during childhood (214, 215) (Fig. 8-21). Their smallness and a loss of fat suggest a search for endocrine dysfunction; the patients often look similar to those who are deficient in growth hormone. The second cardinal feature is disturbed central nervous system development. Children with fetal alcohol syndrome present with a diagnosis of cerebral palsy clinics. The typical child has a small head, a small brain, and delayed motor milestones. Accomplishing fine motor skills is also delayed. Hypotonia is present early, but many develop spasticity later. The typical face has three characteristic features: short palpebral fissures (i.e., the eyes appear small), a flat philtrum (i.e., no groove below the nose), and a thin upper lip (216, 217) (Fig. 8-21). Because of the variety of clinical features, a joint consensus conference sponsored by the Centers for Disease Control suggested that a diagnosis of fetal alcohol spectrum disorder requires all three of the characteristic dysmorphic facial features (smooth philtrum, thin vermillion border, and small palpebral fissures), prenatal or postnatal growth deficit in height or weight, and a central nervous system abnormality.

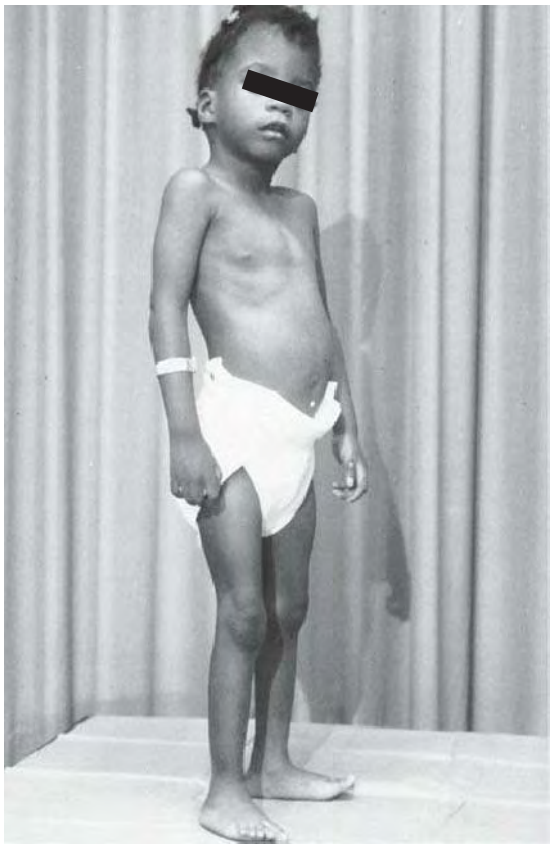


FIGURE 8-21. The 3-year-old patient is small and has the characteristic face of fetal alcohol syndrome. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

Approximately 50% of children with this syndrome have an orthopaedic abnormality, but most of these are not disabling (218–220). At birth, the range of motion is restricted, especially of the hands and feet, and occasionally these contractures are fixed. The contractures typically respond well to physical therapy, although residual stiffness in the proximal interphalangeal joints may remain. Clubfoot is common, and approximately 10% of these patients have developmental dysplasia of the hip. The clubfoot is usually not rigid (221). Cervical spine fusions, usually involving C2 and C3, may be seen on radiographs (220, 222–226). These may resemble the picture seen in Klippel-Feil syndrome, but there are usually none of the other findings associated with that syndrome. Synostoses are also common in the upper extremity, with fusions involving the radial–ulnar articulation and the carpal bones, all without any resultant disability (222, 225, 227). Stippled epiphyses may be seen in the lower extremities, but rarely in the upper extremities (228).

The orthopaedic problems associated with fetal alcohol syndrome can be managed in the same way as in children without this syndrome. The future for children with fetal alcohol syndrome is dim, despite placement away from the alcoholic home. Intellect remains retarded, with little catch up. Social services departments should be involved in these children's care.

VACTERLS and VATER Association. VATER, as the syndrome was previously known, has been expanded to VACTERLS (229). The letters of VACTERLS in this syndrome's name constitute an acronym for the systems and defects involved: vertebral, anal, cardiac, tracheal, esophageal, renal, limb, and single umbilical artery. One does not need to find examples of all seven categories of anomalies in order to diagnose the syndrome. The syndrome can be diagnosed prenatally by visualizing several of the malformations on ultrasound. The most obvious physical finding at birth is the radial ray defect. Between 5% and 10% of radial clubhands are associated with VACTERLS.

The cause is unknown, but it is a nonrandom association, whose simultaneous occurrence by chance is unlikely (230). Disruption of a developmentally important signaling pathway called *Hedgehog* can give all of the clinical findings associated with VACTERLS, suggesting that an intrauterine event disrupting this signaling pathway is the cause (189). The current thought is that these structures are either all formed at the same time, or are all patterned by the same developmental signaling pathway. An event occurring during fetal development that disrupts either the common signaling pathway or any of a variety of susceptible pathways operating at the same time is probably responsible for the associated malformations.

The vertebral defects include disturbed spinal segmentation, with vertebral bars and blocks (231, 232). Thoracic anomalies are worse in those with tracheoesophageal fistula, and lumbar anomalies are more common in those who have an imperforate anus. Occult intraspinal pathology is common (232, 233), and a screening MR study of the spine is recommended, especially in patients who require operative management of their scoliosis. The curves can be managed like other types of congenital scoliosis.

Congenital heart defects are present in one-half of these patients. A ventricular septal defect is the most common problem. Duodenal atresia may be found in this syndrome. The VACTERLS patient often has a single kidney. Other collecting-system anomalies occur frequently among this group.

The limb anomalies range from a hypoplastic thumb to a radial clubhand. The defect may be unilateral or bilateral; bilateral defects are always asymmetric (231). The legs are spared 80% of the time. When the lower extremities are involved, a duplicated hallux is the most common finding.

The normal umbilical cord has two arteries and one vein. The absence of an artery, detectable only at the time of delivery or in the immediate newborn period, reflects the broad range of morphologic defects dating back to placental formation.

Developmental delay may be observed, and is thought to be the consequence of skeletal anomalies of the arms, scoliosis, and surgery for gastrointestinal or genitourinary malformations. Nevertheless, several central nervous system malformations (e.g., encephalocele hydrocephalus) may be associated with VACTERLS, and must be excluded (233, 234). If the patient survives the gastrointestinal anomalies and correction of the cardiac defects, the prognosis for a normal life is excellent. Each orthopaedic abnormality can be treated as an isolated

problem. The sections in this chapter that deal with congenital scoliosis and radial clubhand contain detailed information. The key point is to recognize this association and to identify other abnormalities that might interfere with treatment.

GENES IMPORTANT FOR NERVE OR MUSCLE FUNCTION

There are a large number of neurologic disorders that can be caused by genes that encode for proteins that are important for nerve or muscle function. The course of these disorders is variable; however, several show progressive weakening effects over time. Various inheritance patterns are possible, but frequently these disorders are linked to the X chromosome. Duchenne muscular dystrophy and Rett syndrome are two such disorders that are inherited in an X-linked recessive manner and X-linked dominant manner, respectively.

Familial Dysautonomia. Familial dysautonomia, also called *Riley-Day syndrome*, is an autosomal recessive disorder occurring primarily in Jews who trace their ancestry to Eastern Europe. Among such individuals, the incidence is estimated to be about 1 in 3700. The clinical manifestations are caused by defective functioning of the autonomic nervous system and sensory system. The autonomic dysfunction causes labile blood pressure, dysphagia, abnormal temperature control, and abnormal gastrointestinal motility. Infants have difficulty swallowing, with misdirected fluids going to the lungs, resulting in pneumonia. There is a poor suck response and a curious absence of tears. During childhood, the autonomic dysfunction becomes more apparent, with wide swings in blood pressure and body temperature. There are cyclic vomiting episodes; these crises often last hours or days. Swallowing remains poor. The skin is blotchy. There is relative insensitivity to pain and poor hot–cold distinction. Intelligence is normal, but the children exhibit emotional liability, and may have unusual personality development, especially in the teenage years. The diagnosis is made on clinical findings and on the basis of the presence of five signs: (i) lack of axon flare after intradermal injection of histamine, (ii) absence of fungiform papillae on the tongue, (iii) miosis of the pupil after conjunctival installation of methacholine chloride, (iv) absence of deep tendon reflexes, and (v) diminished tear flow (235–237).

This disorder is caused by a mutation in the inhibitor of kappa light polypeptide gene enhancer in B cells. The protein product of this gene plays a role in the phosphorylation of other signaling proteins, but the mutant form is expressed only in select tissue types, primarily affecting cells in the autonomic nervous system (238, 239). Since the mutation is expressed only in certain tissue types, one approach to treatment would be to change the tissue-specific expression of the mutant form by using drugs that regulate the expression of only the mutant variant. Such a potential treatment has been proposed using tocotrienols, which are members of the vitamin E family (240, 241). Pathologic anatomy reveals a paucity of neurons in cervical sympathetic ganglia, dorsal sensory roots, and abdominal parasympathetic nerves (242). A number of small axons are depleted from the sensory nerves and the dorsal columns. Because of a primary failure to develop axons, the symptoms are present at birth, and there is a loss of nerve cells and progression of symptoms as the patient grows older.

Musculoskeletal manifestations include scoliosis, fracture susceptibility, avascular necrosis, and a Charcot joint–like process. Scoliosis affects a majority of patients, and approximately one-fourth will need operative intervention (243–249). It has an early onset, and progression is often rapid. Kyphosis, accentuated by tight anterior pectoralis muscles, appears in approximately one-half of the patients. Bracing does not work well, because of the underlying gastrointestinal and emotional problems. Anesthesia can be challenging in individuals with such autonomic liability, but with proper techniques, operative intervention is successful. Surgery seems to give better results if performed early in the course of the disease (229, 250, 251).

Fractures occur frequently, and often go unrecognized because of the patient's insensitivity to pain (252). The physician should be suspicious of occult fractures in patients who have had trauma and swelling but experience minimal tenderness. Fractures usually heal quite well, but early diagnosis and avoiding displacement is the goal.

Radiographic evidence of avascular necrosis is common, but the pathobiology is entirely unknown (252–254). There are Legg-Perthes changes in the hips. Osteochondritis dissecans of the knees is often extensive, involving both femoral condyles (Fig. 8-22). It may be difficult to determine whether the ossification changes in the knee are because of osteochondritis dissecans or the early stage of Charcot joint (255, 256). Hip dysplasia may be seen in patients with this syndrome.

The natural history of familial dysautonomia is characterized by a relatively high mortality rate in infancy, attributed to aspiration pneumonia (237). Sudden death in childhood and adolescence occurs because the child is unable to respond appropriately to stress or hypoxia. Early recognition of this syndrome and appropriate care lead to a life expectancy of many decades. Management of the gastrointestinal problems and the use of gastrostomy and fundoplications have been extremely successful in such patients. There have been successful pregnancies brought to term in mothers with the syndrome (257, 258).

Rett Syndrome. Rett syndrome is an X-linked dominant disorder that is present almost exclusively in girls and is characterized by normal development for the first 6 to 18 months, followed by rapid deterioration of higher brain functions. This is accompanied by dementia, autism, loss of purposeful use of the hands, and ataxia. After the initial rapid decline, the deterioration slows dramatically, so that affected individuals may have a relatively stable picture for several decades (244). There is variability in the severity of the decline, so that some girls are still walking as teenagers, whereas others stop ambulating in early childhood (245). A hand radiograph may help with

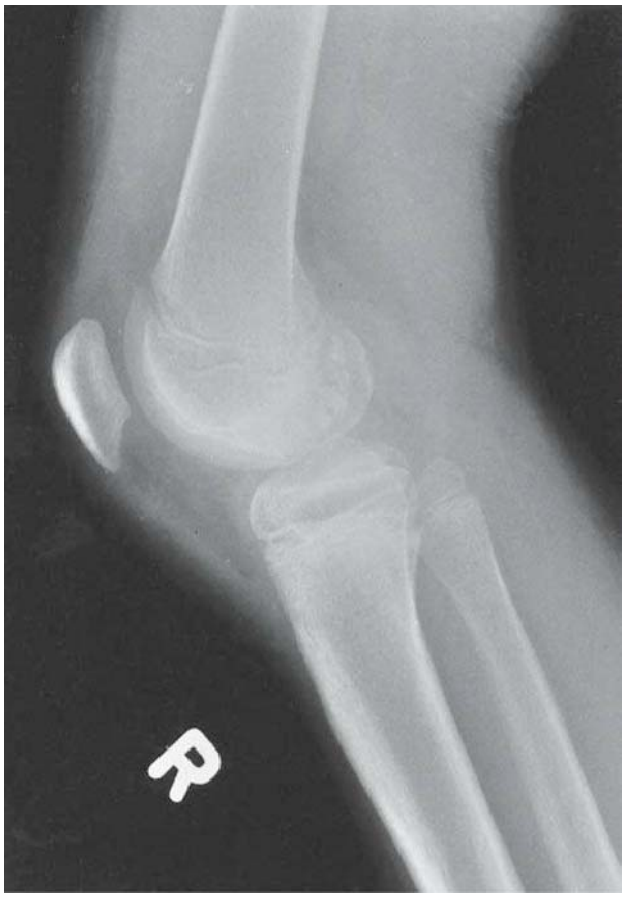


FIGURE 8-22. Familial dysautonomia. Irregular ossifications of the distal femoral epiphysis mimic osteochondritis dissecans.

the diagnosis, because 60% will have either a negative ulnar variance or a short fourth metacarpal (246, 247).

Children with this syndrome were initially thought to have cerebral palsy with a movement disorder. Andreas Rett, a pediatrician practicing in Austria, noted that these girls all had normal development in the first month of life, and was thus able to separate them from those with cerebral palsy. It occurs with an incidence of 1 in 40,000. In some patients, it is caused by a mutation in the *MECP2* gene, which encodes X-linked methyl-CpG-binding protein 2. This protein plays an important role in regulating gene expression during development, especially in the central nervous system (259). X-linked dominant diseases are more severe in boys, and Rett is probably fatal in the vast majority of male patients, though few such cases have been reported (260). Genetic testing and prenatal diagnosis (261) are possible, but as in other syndromes, a careful physical examination and history can be used to make the diagnosis in most cases (262).

Children with Rett syndrome present to the orthopaedist with a clinical picture similar to that of a cerebral palsy patient with total body involvement. Scoliosis occurs in over half the girls who are affected with this disorder (260, 263–266). Orthotic management probably does not alter the progression of the curve. There is a typical, usually long "c" pattern to the curves. These can be stabilized surgically when they reach a magnitude that interferes with sitting or balance. Although case series suggest an improvement after surgery (262), as is seen in cerebral palsy, there are no comparative studies showing improved function after spinal surgery. Spinal instrumentation and fusion should include the whole curve and any kyphotic segments. Although, theoretically, walking ability can worsen following extensive fusions, this has not been reported in the small number of cases in which spinal surgery was undertaken in ambulatory girls with Rett syndrome (259, 262, 263). Coxa valga and lower extremity contractures can occur, and these should be managed as in cerebral palsy, with emphasis placed on operative procedures that will improve function or decrease pain (264, 266, 267).

The life span in Rett syndrome is not known, but there are some affected individuals with a normal life span. There are a variety of nonorthopaedic problems, including cardiac conduction abnormalities, epilepsy, and vasomotor instability of the lower limbs. Some of these put the patients at increased risk when undergoing anesthesia (268). Interestingly, there is a high incidence of left handedness (approximately 40%) in girls with Rett syndrome (269).

CHROMOSOMAL (MULTIPLE GENES)

Chromosomal abnormalities involve large portions of DNA, and multiple genes are affected. There can be deletions, duplications, or translocations. Large abnormalities in chromosomes are almost always associated with some degree of mental deficiency. Because there is duplication of multiple genes, there are multiple abnormalities in multiple organ systems. Since multiple genes are abnormal in all cells, normal cell functions (such as the ability to mount an immune response or normal wound healing) also may be abnormal. Except for rare instances, these disorders are not inherited, and occur as sporadic events.

Down Syndrome. Down syndrome is the most common and perhaps the most readily recognizable malformation in humans (270) (Fig. 8-23). Patients have a characteristic facial appearance including upward-slanting eyes, epicanthal folds, and a flattened profile. Examination of the hands reveals a single flexion crease, often referred to as a *simian crease*. There is also clinodactyly of the small finger. These hand malformations have no clinical significance (271). Milestones are delayed, with most children not walking until 2 to 3 years of age. The classic gait pattern is broad based, toed out, and waddling.

The bones in Down syndrome have subtle malformations. The best-studied changes are in the pelvis, which is characterized by flat acetabula and flared iliac wings (243). These pelvic changes are so characteristic that prior to use of chromosome analysis, pelvic radiographs were used for confirming the diagnosis. Short stature is a cardinal feature; the average for men is 155 cm (61 in.), and the average for women is 145 cm (57 in.) (244). The detection of bone changes can be useful in prenatal

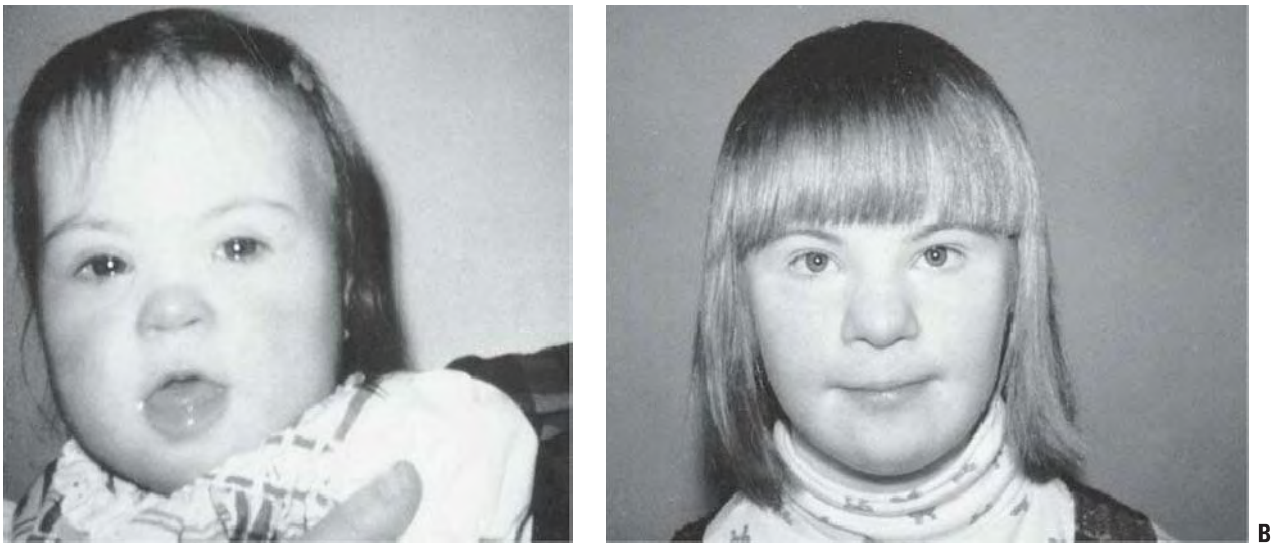


FIGURE 8-23. Down syndrome. The child has the characteristic face, with upward-slanting eyes, epicanthal folds, open mouth of early childhood, and flattened profile. **A:** At 1 year of age. **B:** At 10 years of age. (A, Courtesy of Murray Feingold, MD, Boston, Massachusetts. B, From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

diagnosis. A combination of bone length and lab tests on the mother (human chorionic gonadotropin and alpha-fetoprotein levels) may predict the diagnosis, although the positive and negative predictive values are not as good as had been initially hoped (245). Cytogenetic study, which identifies complete trisomy 21 in 95% of the cases, remains the best confirmative test.

Complete trisomies account for 95% of the cases, with 2% mosaics and 3% translocations. The overall occurrence is 1 per 660 live births, and the incidence is closely related to maternal age. If the mother is younger than 30 years of age, the risk is 1 of 5000 live births, and if the mother is older than 35 years of age, the incidence rises to 1 in 250. The critical region for Down syndrome resides in part of the long arm of chromosome 21. Duplication of a 5-megabase region of chromosome 21 (located at 21q22.2–22.3) causes the classic phenotypic features, such as the characteristic facies, hand anomalies, congenital heart disease, and some aspects of mental retardation (246). This region probably contains a number of genes whose duplication is necessary to produce the syndrome.

The general features of Down syndrome are well known. There is a characteristic flattened face. Mental retardation is typical, but performance is far better than expected from standard IQ testing. Congenital heart disease occurs in about 50% of patients and is usually a septal defect (e.g., arteriovenous communis, ventricular septal defect). Duodenal atresia is found regularly. Leukemia occurs in about 1% of this population (1, 5). There is a high incidence of endocrinopathies, hypothyroidism in particular. Infections are common, and while the precise molecular mechanism is not apparent, it may be due to the same white blood cell abnormality that predisposes to leukemia. The propensity to develop infections may result in a higher than anticipated rate of surgical wound infections (225). Although problems with fracture repair have not been reported, there is a substantially worse than expected rate of successful arthrodesis in procedures to obtain a surgical fusion, suggesting a defect in osteoblast function (226). The appearance of premature aging is obvious, and there is often an early onset of Alzheimer disease (247).

Approximately 10% of individuals with Down syndrome show an increased atlantodens interval on lateral spine films (248, 249, 272–274) (Fig. 8-24A). In most, the increased interval is not associated with symptoms (249, 275). In addition, there is a broad array of other abnormalities in the upper cervical spine, including instability at occiput and C1 (274, 276–278), odontoid dysplasia (249, 279–281) (Fig. 8-24C), laminal defects at C1 (282) (Fig. 8-24B), spondylolisthesis (Fig. 8-24D), cervical stenosis (235), and precocious arthritis in the midcervical region (283, 284) (Fig. 8-24E). In addition, there is an anomalous course to the vertebral artery at the craniovertebral junction, which can complicate surgical management (238). The cervical spine abnormalities may complicate anesthesia (239).

These other abnormalities often complicate decision making about spinal instability. Although routine screening radiographs often disclose these cervical spine abnormalities, radiographs are not reliable in predicting myelopathy (285–291). Therefore, their efficacy in the management of the cervical spine in patients with Down syndrome is uncertain. The management of cervical instability in Down syndrome is discussed elsewhere in this text.

Approximately 50% of patients with Down syndrome have scoliosis, with an idiopathic pattern in most (292). Scoliosis is five times more likely to be detected in a severely retarded, institutionalized population than in an ambulatory

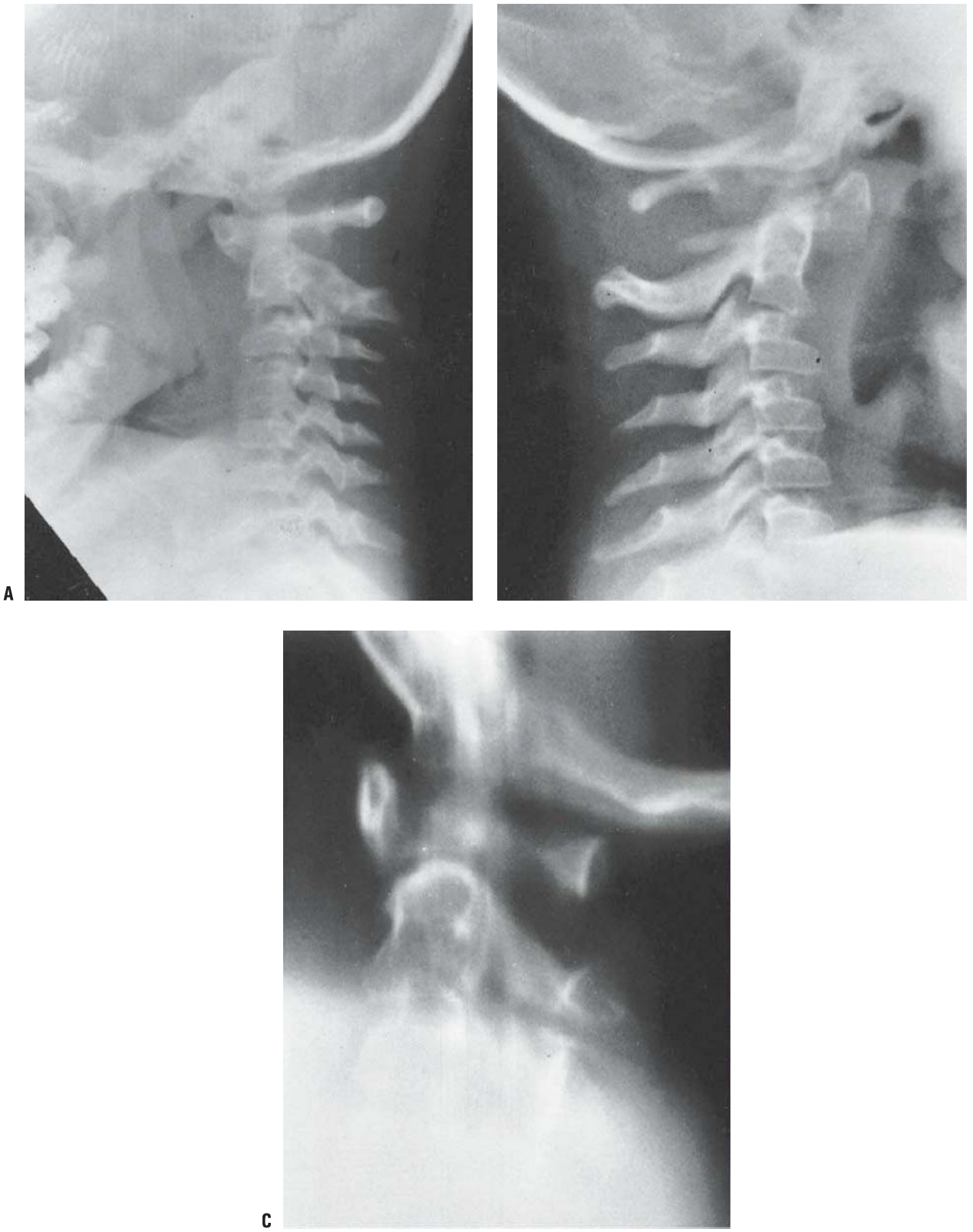


FIGURE 8-24. Cervical spine abnormalities in a patient with Down syndrome. **A:** Atlantodens instability at 8 years of age. **B:** Hypoplastic posterior elements of C1 at 3 years of age. **C:** Os odontoideum and increased atlantodens interval at 14 years of age.

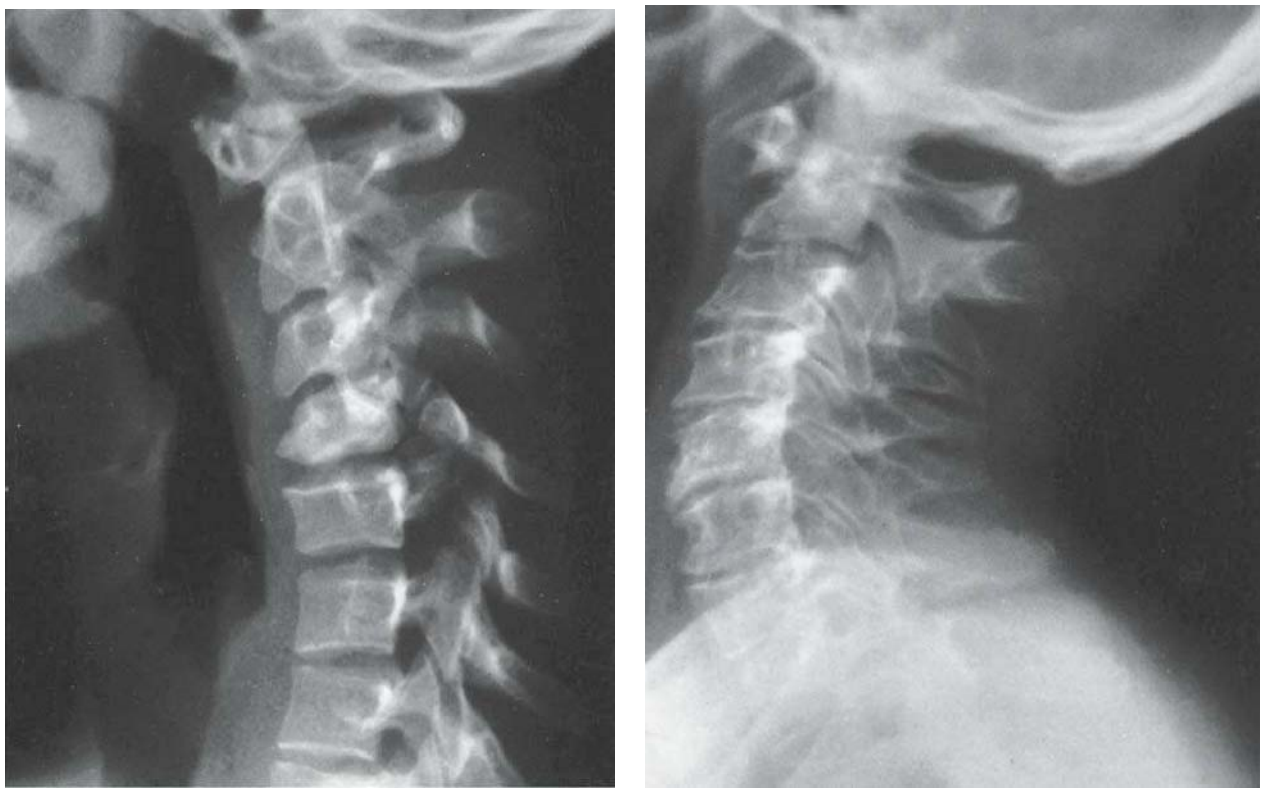


FIGURE 8-24. (*continued*) **D:** Midcervical spondylolysis at 16 years of age. **E:** Precocious osteoarthritis of the midcervical spine at 40 years of age. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

setting. This finding raises the possibility that factors such as severity of the phenotype, or other neuromuscular factors contribute to scoliosis. Management is the same as in idiopathic scoliosis. Similar to the case of the cervical spine, there is a higher rate of complications from scoliosis surgery than in the general population (293). Spondylolisthesis occurs in about 6%, with the lower lumbar spine being most commonly involved. Spondylolisthesis can also occur in the cervical spine.

Congenital dislocated hips are rare, but progressive dysplasia may begin during later childhood. This loss of acetabular containment may lead to an acute or a gradual complete dislocation (Fig. 8-25A,B). The onset of acetabular dysplasia can be progressive even after maturity, leading to dislocations in adulthood (294–296) (Fig. 8-25C,D). Although hip instability and developmental dysplasia are thought to lead to functional disability (interfering with walking and reducing independent mobility), there are no studies showing this to be the case. The etiology of the hip instability is probably multifactorial, with ligamentous laxity, subtle changes in the shape of the pelvis and acetabular alignment, and behavior (some children become habitual dislocators) all contributing. Treatment of the unstable hip is difficult, and the multiple causative factors also contribute to higher treatment failure rates. Both operative and nonoperative treatment are reported. Prolonged bracing after reduction for the hip that dislocates acutely has shown success in children younger than 6 years (297). In cases in which there are repeated dislocations, surgical reconstruction is warranted, especially in children older than 6 years. Operative treatment requires correction of all the deforming factors. Reconstruction must take into account the abnormal bone alignment, and should include femoral and acetabular osteotomies, as well as imbrication of the redundant capsule. Posterior acetabular deficiency has been reported, and was not improved following a traditional Salter-style innominate osteotomy (298); therefore, three-dimensional imaging (such as a CT scan) should be considered before embarking on surgery. The recurrence rate following hip surgery is high, suggesting that other factors related to the underlying disease, but not necessarily related to the hip anatomy itself, are contributory (299–301).

Slipped capital femoral epiphyses are reported in all Down syndrome series, although the precise incidence is unknown (292, 302) (Fig. 8-26). There appears to be a higher-than-expected risk for avascular necrosis. The reasons are not clear, but factors include more acute slips and delayed diagnoses. It is tempting to speculate about an association with the hypothyroid state, which is common in Down syndrome. All children with Down syndrome should have thyroid function tests.

The configuration of the knee is that of genu valgum, with a subluxed and a dislocated patella (Fig. 8-27). Many individuals will have asymptomatic patellar dislocations that do not require treatment (303). Symptomatic cases should be

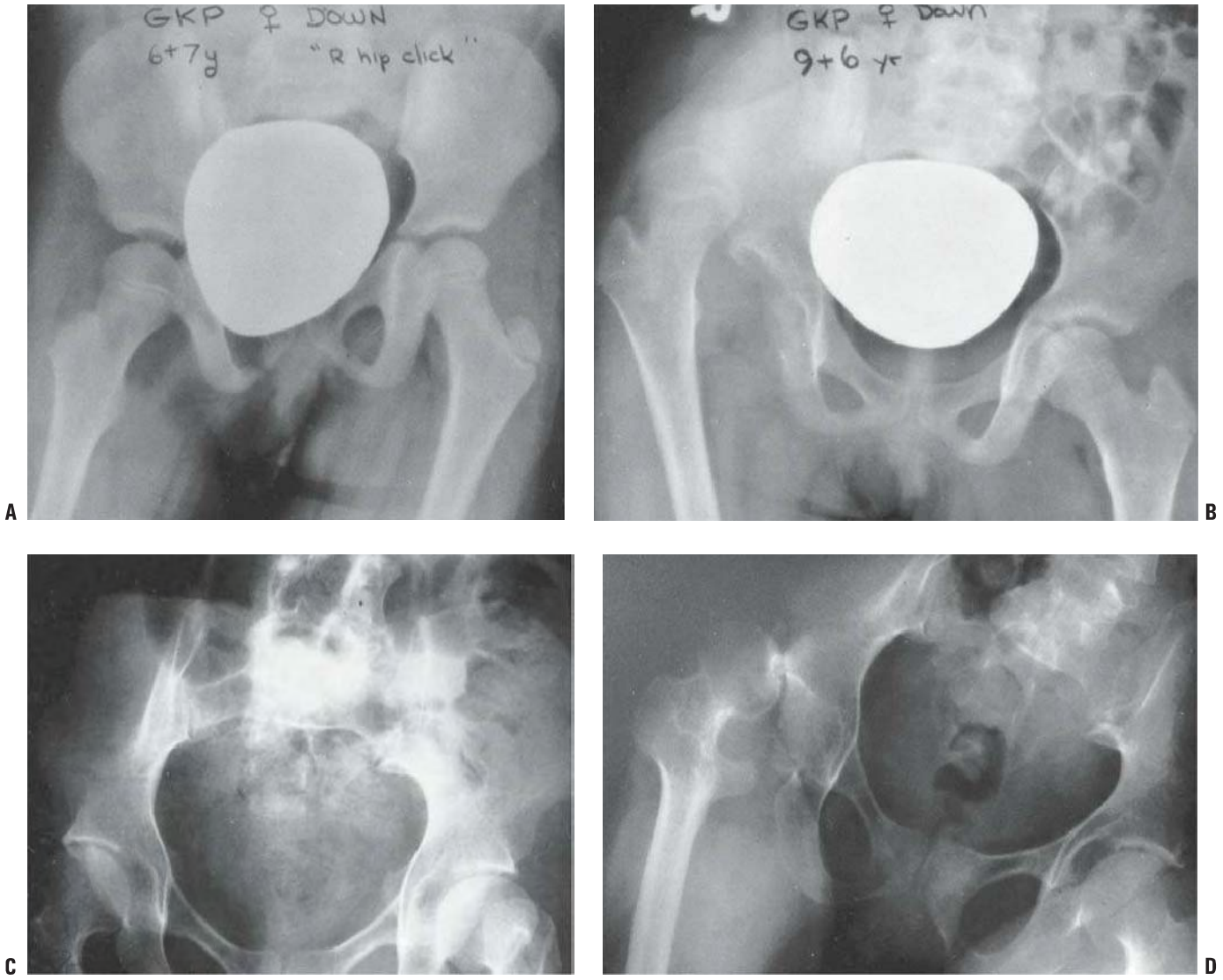


FIGURE 8-25. Down syndrome patient with late-onset developmental dysplasia of the hip and dislocation. **A:** Pelvic radiograph taken in standing position, at 6.5 years of age. **B:** At 9.5 years of age, the patient suddenly refused to walk because of hip dislocation. **C:** Pelvic radiograph of a 31-year-old man with Down syndrome. **D:** Three years later, dislocation of right hip occurred. (A and B, from Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987; C and D, from Pueschel SM. Should children with Down syndrome be screened for atlantoaxial instability? *Arch Pediatr Adolesc Med* 1998;152:123, with permission.)

initially managed with orthoses and a physiotherapy program. Individuals who continue to be symptomatic can be considered for operative treatment. As in hip dysplasia, operative interventions that correct all of the deformities (bone and soft tissue) have the best success.

The characteristic appearance of the feet in childhood is one of an asymptomatic flexible planovalgus shape, with an increased space between the great and the second toes. Because it is important to maintain mobility in adults with Down syndrome, symptomatic foot problems should be treated. The treatment involves footwear modification in many cases, but may require surgery in cases that are symptomatic despite appropriate footwear. Valgus feet with toe deformities are most likely to become symptomatic. In many, hallux valgus develops in adolescence, and in adulthood the bunions become symptomatic. Orthotics will improve foot position, but may actually slow the walking speed of children with Down syndrome (304). For that reason, orthotics should be used only in symptomatic cases. Repair of a hallux valgus and bunion may be needed in late adolescence or young adulthood. Because of the hindfoot valgus, pronation, and external tibial torsion, the forces that produce bunions are obvious, and fusion of the first metatarsophalangeal joint should be considered, along with osteotomy, to correct hindfoot valgus.

A polyarticular arthropathy occurs in approximately 10% of those with Down syndrome (305–307). Whether this is true juvenile rheumatoid arthritis or a unique inflammatory arthritis due to genetic or immune defects is unknown; the natural history is not documented. Delayed diagnosis is common. Nonsteroidal anti-inflammatory drugs have been the mainstay

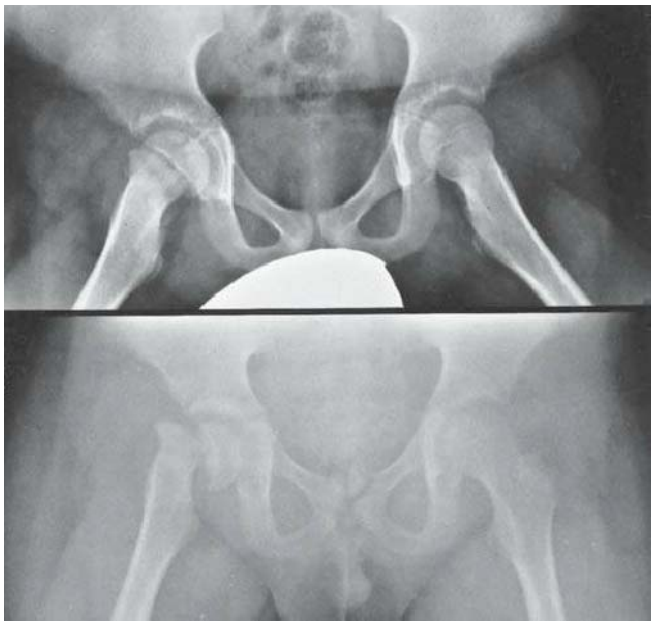


FIGURE 8-26. Effects of Down syndrome in a 12-year-old boy with 4 months of knee pain. The grade I slipped capital femoral epiphysis progressed to a total slip while the patient was undergoing preoperative evaluation and bed rest. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

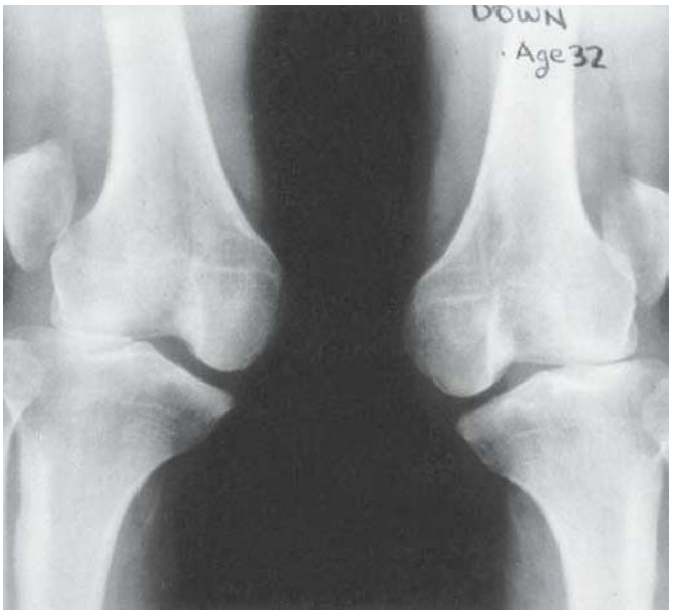


FIGURE 8-27. Effects of Down syndrome in a 32-year-old patient. The radiograph shows bilateral dislocated patellae and an oblique orientation of the joint line. The patient is fully ambulatory, but before standing must manually reduce the patellae to the midline. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

of treatment. Foot symptoms are exceptionally frequent with the onset of polyarthropathy (Fig. 8-28). Patients with Down syndrome have low bone mineral density, but it is in part a consequence of reduced body size, relative physical inactivity, and low vitamin D levels from a lack of sunlight exposure. As such, it is recommended that patients with Down syndrome engage in regular physical activity and have sufficient levels of vitamin D (256).

Marked joint hypermobility is evident; the children are able to assume the most intriguing sitting postures. Ligamentous laxity was traditionally thought to be the cause of joint hypermobility, and it was assumed that it predisposes patients with Down syndrome to orthopaedic pathology. However, ligamentous laxity correlates poorly with joint hypermobility. This suggests that other factors, such as subtle malformations in the shapes of bones and insertion sites of ligaments, play a role in hypermobility (308, 309).

The natural history of those with Down syndrome has changed in the last few decades. Longevity has increased because of the aggressive surgical approach to congenital heart disease, chemotherapy for leukemia, and antibiotics for infection. Survival into the sixties is common. Approximately one of five persons with Down syndrome has musculoskeletal abnormalities. Many of these, however, are merely radiographic abnormalities or curious physical findings. These patients often have excellent functional performance despite the abnormalities. There is a paucity of well-documented, long-term orthopaedic studies of patients with Down syndrome. Treatment programs should focus on functional performance rather than on radiographic findings.

Turner Syndrome. Turner syndrome is present only in girls, and consists of short stature, sexual infantilism, a webbed neck, and cubitus valgus. It is a relatively common chromosome disorder affecting 1 in 2500 live births, but the rate of intrauterine lethality is 95%. The syndrome is caused by a single X chromosome. In two-thirds of cases, all cells are XO,

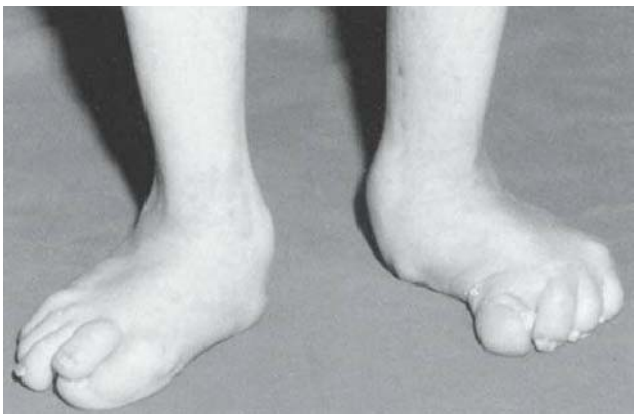


FIGURE 8-28. Polyarthritis of Down syndrome and valgus feet led to significant deformity in a 16-year-old patient. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

and parental origin of the single X chromosome is the mother in 70% of the cases (310). XO mosaicism occurs in about one-third of patients, and in 1% there is deletion of only a part of an X chromosome (310, 311). Cytogenetic studies will confirm this diagnosis.

The effect of the single X chromosome may be different, depending on whether it is derived from the father or from the mother, and this is probably the result of imprinting (285). Recent studies based on individuals with partial loss of the X chromosome suggest that a critical region at Xp11.2–p22.1 is responsible for the disease (312).

The identification of particular features at a particular age raises suspicion of the presence of this syndrome. At birth, the child has a webbed neck, widely spaced nipples, and edema of the hands and feet. The foot edema may persist for several months. During childhood, the low hairline, webbed neck, cubitus valgus, and short stature become more apparent. The adolescent has short stature and sexual infantilism. The most important features that call for chromosome analysis are edema of the hands and feet at birth, short stature in childhood, and sexual infantilism as an adolescent.

Growth retardation is a cardinal feature, with an ultimate height of approximately 140 cm (56 in.) (286). Bone maturation is normal until 8 to 9 years of age; then, because sex hormone stimulation is absent, there is neither skeletal maturation nor pubertal growth spurt. There is no puberty at all, and the girls remain without secondary sexual characteristics unless exogenous estrogen is administered.

The web neck looks like a feature of Klippel-Feil syndrome, but the cervical spine radiographs are normal. It is a cutaneous web only, and the cause may be related to an intrauterine cystic hygroma (313). It is cosmetically unsightly, and plastic surgery is effective (314).

Scoliosis is common, present in over 10% of affected individuals (315), and the curve usually develops in juveniles. The delayed skeletal maturation allows a long period for curve progression. Growth hormone, which is almost always administered to girls with this syndrome, accelerates curve progression. Although the scoliosis can be managed in the same way as idiopathic scoliosis, patients must be observed more frequently during growth hormone administration. Kyphosis is present in a large proportion of individuals with this condition, but its functional significance is unclear (287).

Cubitus valgus is present in 80%, but there is a normal range of elbow motion and no disability (316). Genu valgum is also apparent, but the vast majority of cases are asymptomatic. Osteotomy is performed for the rare symptomatic case. There is a medial bony protuberance not unlike an osteochondroma, arising off the proximal tibia in some patients (317).

Osteoporosis is a significant problem because of the low estrogen and an altered renal vitamin D metabolism, which may correctable with the administration of adequate calcium, vitamin D, growth hormone, and sex steroid supplementation (270, 288, 289, 318). These measures work best to maintain bone density, rather than to increase it from pathologic levels, and as such should be instituted early in the course (243, 271). While a high incidence of wrist fractures has been reported in childhood (290), in women who are treated with treated with standard estrogen therapy there is not a higher fracture rate (245).

Intelligence is normal, but there is a high frequency of learning disabilities (291, 319). The life expectancy is normal, overall medical status is excellent, and social acceptance is good (320). There are some heart and kidney abnormalities reported at a somewhat higher incidence than for the normal population (321). Having only one X chromosome enables the patient to have X-linked recessive disorders, such as Duchenne muscular dystrophy.

Children with Turner syndrome are treated with growth hormone through adolescence, which results in a modest increase in growth velocity and final height from an average of 140 cm (55 in.) to just under 149 cm (58.5 in.) (322, 323). Limb lengthening is associated with a very high rate of complications, and is therefore not recommended (324). Cyclic sex hormones are administered during adolescence and throughout adulthood. Estrogen is necessary for the development of secondary sexual characteristics, and the estrogens, and possibly the previously administered growth hormone, help prevent osteoporosis. Many with Turner syndrome marry, and obstetric techniques of hormone supplementation and ovum transplantation can result in pregnancy.

Noonan Syndrome. Although Noonan syndrome is not caused by a chromosomal abnormality, its phenotype is reminiscent of Turner syndrome, with short stature, webbed neck, cubitus valgus, and sexual immaturity (325, 326), which is why it is discussed here. Noonan syndrome is an autosomal dominant disorder, in which approximately half of all cases are caused by a mutation in the *PTPN11* gene, which encodes for a protein—tyrosine phosphatase (327–329). How tyrosine phosphatase causes the observed phenotype has yet to be elucidated. The incidence is between 1 in 1000 and 1 in 2500 (330). Many clinical features are shared with the Turner phenotype, but what distinguishes this syndrome are the normal gonads, a high incidence of mental retardation, and right-sided congenital heart defects, often with hypertrophic cardiomyopathy (331, 332). Scoliosis is more common (40%) than in patients with Turner syndrome, and more severe (333, 334). Minor to major vertebral abnormalities may be seen on radiographs. Skeletal maturation is delayed despite normal puberty and menarche. There is short stature, and the use of growth hormone may be associated with a modest increase in ultimate height (305); however, there are no well-controlled comparative series on the basis of which to evaluate the use of growth hormone in these children. Noonan syndrome is often misdiagnosed, and most frequently confused with King-Denborough syndrome, a myopathic arthrogryposis syndrome characterized by short stature, web neck, spinal deformity, and contractures. Recognizing the difference is important, because a malignant hyperthermia-like picture is part of the King-Denborough syndrome. The use of genetic testing for *PTPN11* mutations may aid in this differentiation.

Trichorhinophalangeal Syndrome. The name *trichorhinophalangeal* (TRP) *syndrome* causes confusion, because textbooks describe trichorhinophalangeal syndrome, trichorhinophalangeal syndrome with exostosis, and Langer-Giedion syndrome. It is best to think of two relatively distinct TRP syndromes: types I and II. Despite the clinical overlaps between the two, there are enough features to separate them into distinct syndromes.

Patients with TRP-I have a pear-shaped, bulbous nose, prominent ears, sparse hair, and cone epiphyses. They have mild growth retardation. The thumbs are broad, and the fingers are often angled at the distal interphalangeal and proximal interphalangeal joints. The hips mimic a Perthes-like disease in radiographs and symptoms (306). There may be lax ligaments.

The key feature distinguishing TRP-II from TRP-I is the presence of multiple exostoses, especially involving the lower extremities. Those with TRP-II have facial features and cone epiphyses similar to patients with TRP-I. There is a higher chance of mental retardation in TRP-II. Langer-Giedion syndrome and TRP-II are identical (307). Patients with TRP-II also have microcephaly, large and protruding ears, a bulbous nose, and sparse scalp hair. In infancy, their skin is redundant and loose, and this condition may be severe enough to mimic EDS. Marked ligamentous laxity may further support this error in diagnosis. There is a tendency toward fractures. Similar to TRP-I, the Perthes-like picture, as well as the hand anomalies, are present in TRP-II (335).

Both TRP-I and TRP-II are due to mutation or loss of the *TRSP1* gene (307). However, TRP-II is due to a larger loss of the chromosomal region, with loss of the adjacent gene, *EXT-1*, as well. The *EXT-1* gene is one of the genes responsible for hereditary exostoses, and this explains the exostoses associated with TRP-II. The *TRSP1* gene is responsible for the facial malformation and cone epiphyses present in both disorders. Individuals with loss of a large portion of a chromosome are more likely to have mental retardation. This explains the mental retardation in some patients with TRP-II, which is characterized by a larger region of chromosomal deletion. TRP-II is one of the few disorders actually known to be due to two contiguous genes (5).

Radiographically, the hand of a patient with TRP-I or TRP-II shows short fourth and fifth metacarpals, cone epiphyses, a short and broad thumb, and fingers with angled proximal and distal interphalangeal joints (336) (Fig. 8-29). The cone epiphyses, so characteristic of this syndrome, are not seen until after 3 or 4 years of age. The pelvis shows the unilateral or bilateral changes of Perthes in TRP-I and TRP-II, but rather than resolution, the Perthes-like picture persists, evolving into a pattern more like multiple epiphyseal dysplasia with precocious arthritis (Fig. 8-30). Despite the wealth of radiographic abnormalities, the hands rarely have functional disturbances. Osteotomy of the thumb is occasionally needed. If symptomatic, we recommend managing the hips as in symptomatic Perthes, but there is insufficient information available about outcomes. Occasionally, an exostosis may be large or symptomatic enough to require excision.

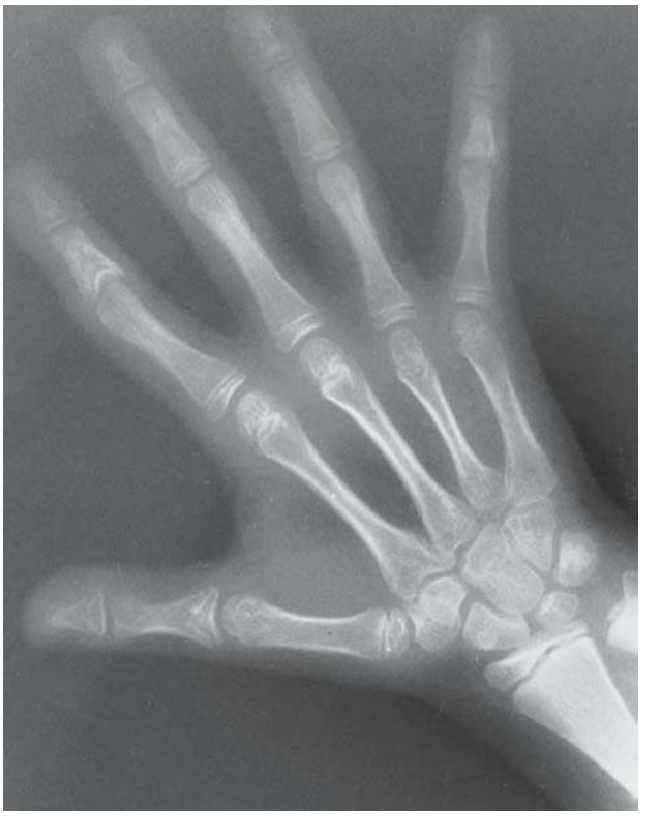


FIGURE 8-29. Trichorhinophalangeal syndrome. This 11-year-old patient has cone- or chevron-shaped epiphyses in the hand, and a broad thumb and distal phalanx.

Prader-Willi Syndrome. Prader-Willi syndrome is characterized by hypotonia, obesity, hypogonadism, short stature, small hands and feet, and mental deficiency (337–339). The incidence is 1 in 5000 births. As newborns, those with Prader-Willi syndrome are floppy babies, having hypotonia, poor feeding, and delayed milestones (340). The symptoms may mimic those of infants with spinal muscular atrophy. Approximately 10% of infants have developmental dysplasia of the hip. The syndrome may be remembered with an "H" mnemonic: hypotonia, hypogonadism, hyperphagia, hypomentation, and small hands, all probably based on a hypothalamic disorder.

After 1 or 2 years of age, a different clinical picture appears (341). A characteristic face of upward-slanting, almond-shaped eyes becomes apparent (Fig. 8-31). Obesity begins, and a Prader-Willi diagnosis is usually suspected because of the onset of a voracious eating disorder. The patient has a preoccupation with food and an insatiable appetite (342, 343). Obesity has a central distribution, sparing the distal limbs. Complex behavioral modification programs are occasionally effective. Affected individuals have short stature, below the 10th percentile, with an ultimate height of 150 cm (59 in.). There is no adolescent growth spurt. The genitalia are hypoplastic, and the patient has small hands and feet (344). Mental retardation is present, but it is extremely variable (342, 345).

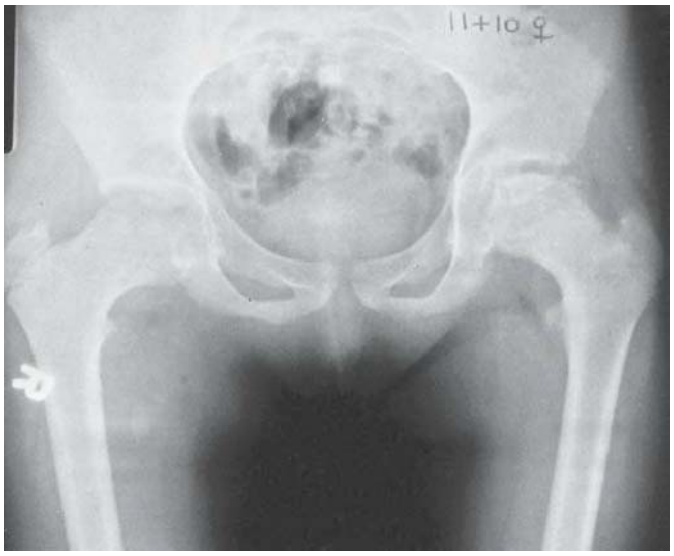


FIGURE 8-30. Trichorhinophalangeal syndrome, type I. The changes mimic Legg-Perthes disease, but by 12 years of age they did not resolve. On the right is a small but spherical epiphysis. On the left, the changes are similar to those seen in Perthes disease and in multiple epiphyseal dysplasia.

Prader-Willi syndrome is caused by a deletion of a small part of chromosome 15 (15q11–13) of paternal origin (346, 347). This is an example of genomic imprinting, because only missing DNA from the father causes the syndrome (348). Genomic imprinting is a process by which genes of maternal origin have different effects from genes of paternal origin. Angelman syndrome, or happy puppet syndrome, is phenotypically dissimilar to Prader-Willi syndrome. Angelman syndrome patients are small and mentally retarded, and they have athetosis and seizures. However, they have the exact chromosome deletion that occurs in Prader-Willi syndrome (15q11–13), except that the deleted DNA is of maternal origin (347).

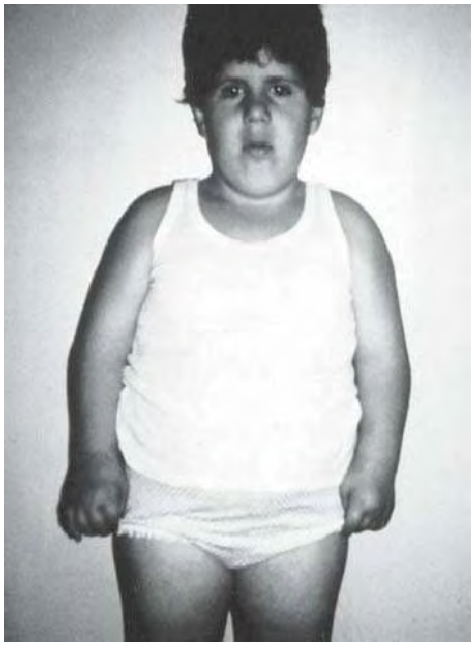


FIGURE 8-31. Prader-Willi syndrome in a 7-year-old patient. The features include truncal obesity and a round face with almond-shaped eyes. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

Several series show that growth hormone improves body composition, fat utilization, and physical strength and agility and as well as growth (286, 349, 350). Despite this information, decisions about the use of growth hormone in this condition are confounded by reports of deaths of children with Prader-Willi syndrome who were given growth hormone. However, it is not known whether these deaths were actually related to growth hormone, or whether the children succumbed to other manifestations of the syndrome (351, 352).

The most significant orthopaedic problem is juvenile-onset scoliosis, which affects roughly half of patients (Fig. 8-32) (353). It is difficult to control with an orthosis because of the truncal fat (354–357). Children with kyphosis associated with scoliosis have a higher change of requiring surgery (353), Those who come to surgery have a higher anesthesia risk because of morbid obesity (358), and there is a higher complication rate to surgery itself (312). While growth hormone was thought to cause worsening of scoliosis progression, a recent randomized trial shows that this is not the case, and as such one should not use the presence of scoliosis as a rationale to avoid growth hormone treatment (286). While a number of other orthopaedic conditions are reported, genu valgum and pes planus are reported most commonly. These have limited or no effect on functional health and physical performance, and as such does not require intervention. While hip dysplasia is present at a higher rate than in the general population, SCFE is not, intriguingly suggesting that endocrinopathy and excess weight alone is not enough to cause a slip of the proximal femoral epiphysis (313).

Rubinstein-Taybi Syndrome. The Rubinstein-Taybi syndrome is characterized by mental retardation associated with characteristic digital changes, consisting mainly of broad thumbs and large toes (359). It is relatively common among mentally retarded persons, with an incidence of 1 in 500 (327). Most cases are sporadic, although there is the possibility of autosomal dominant inheritance (328).

One of the most characteristic clinical features is a Cyrano de Bergerac–like nose with the nasal septum extending below the nostrils (Fig. 8-33). These facial characteristics may change with time, making this a less reliable finding (329). Broad terminal phalanges of the thumb are present in 87% of patients, and the great toe is affected in all patients. One-half of the patients have radially angulated thumbs, and this causes disability. Hallux varus is common, and the physician should consider Rubinstein-Taybi syndrome whenever congenital hallux varus is encountered. Patients have ligamentous laxity and pronated feet, and an increased incidence of fractures (327).

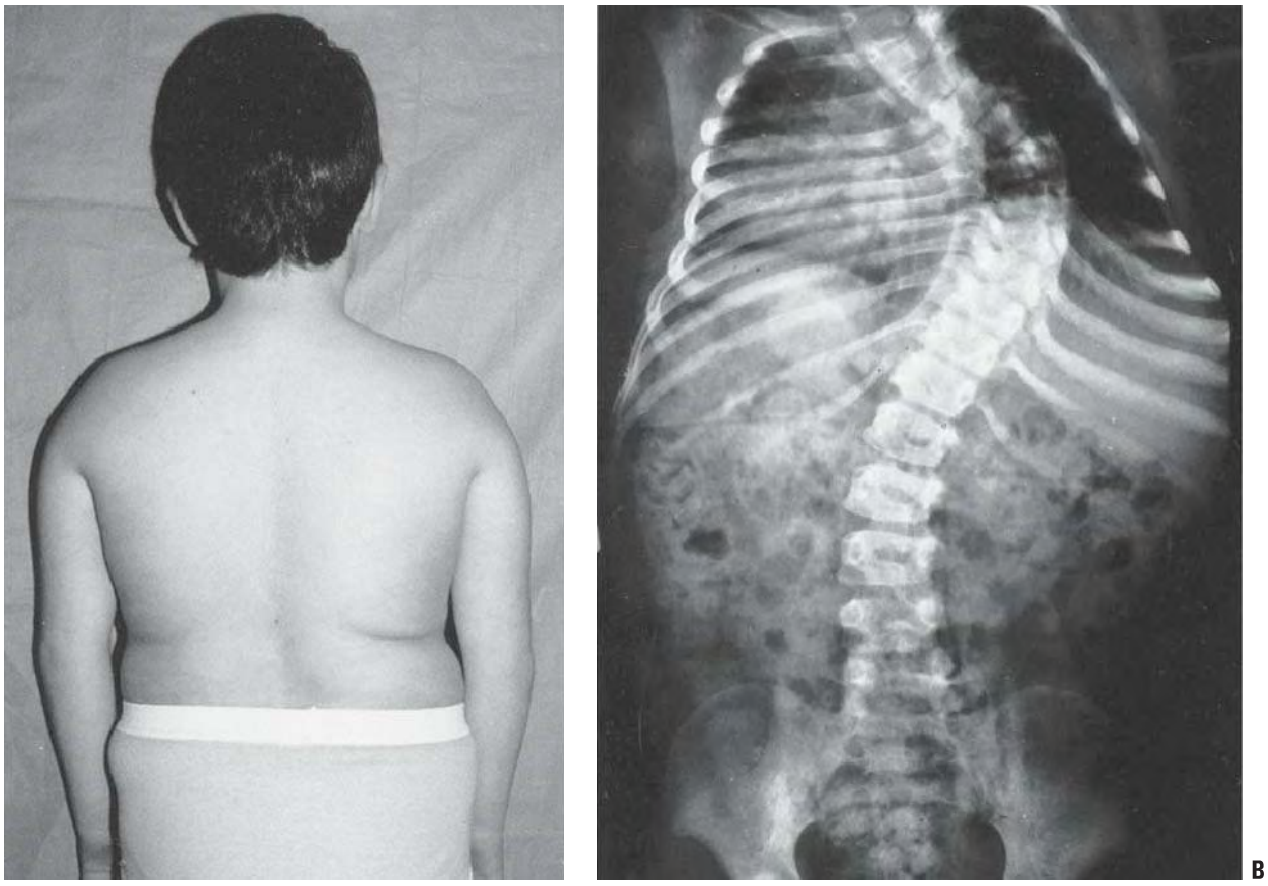


FIGURE 8-32. Prader-Willi syndrome in a 6-year-old patient. **A:** Scoliosis is difficult to detect because of the truncal obesity. **B:** The roentgenogram of this patient discloses a 50-degree thoracic curve. (**B** from Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

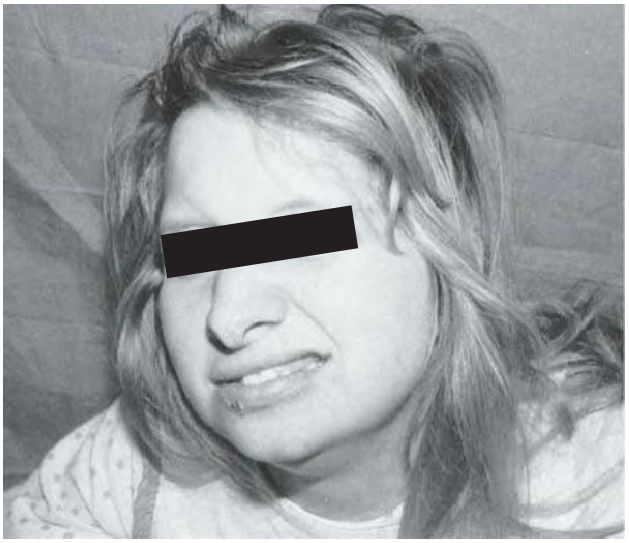


FIGURE 8-33. Rubinstein-Taybi syndrome. In a 10-year-old girl, the characteristic Cyrano de Bergerac–like nose has a septum that extends below the nostrils.

The radiographs are rather characteristic. The thumb shows a wide distal phalanx, with soft-tissue hypertrophy and a triangular proximal phalanx (i.e., delta phalanx) that accounts for the radial deviation (Fig. 8-34). The toe demonstrates duplicated or broad distal phalanx, but true polydactyly is not part of this syndrome (Fig. 8-34B). There is an assortment of other insignificant skeletal anomalies, many in the axial skeleton (360).

Patients with Rubinstein-Taybi syndrome have been shown to have breakpoints in, and microdeletions of, chromosome 16p13.3. This region contains the gene for CREB-binding protein, a nuclear protein participating as a coactivator in cyclic-AMP–regulated gene expression. This protein plays an important role in the development of the central nervous system, head, and neck, and this explains the facial malformation and mental retardation associated with this syndrome. The propensity to develop tumors in these regions is probably caused by malregulation of cyclic-AMP–regulated gene expression (361).

Birth weight and size are normal, but growth retardation is noticed at the end of the first year, and there is no true pubertal growth spurt (362). The patients are mentally retarded, many with microcephaly. IQ can range from 35 to 80, with a delay in acquiring skills. However, these features vary. Associated

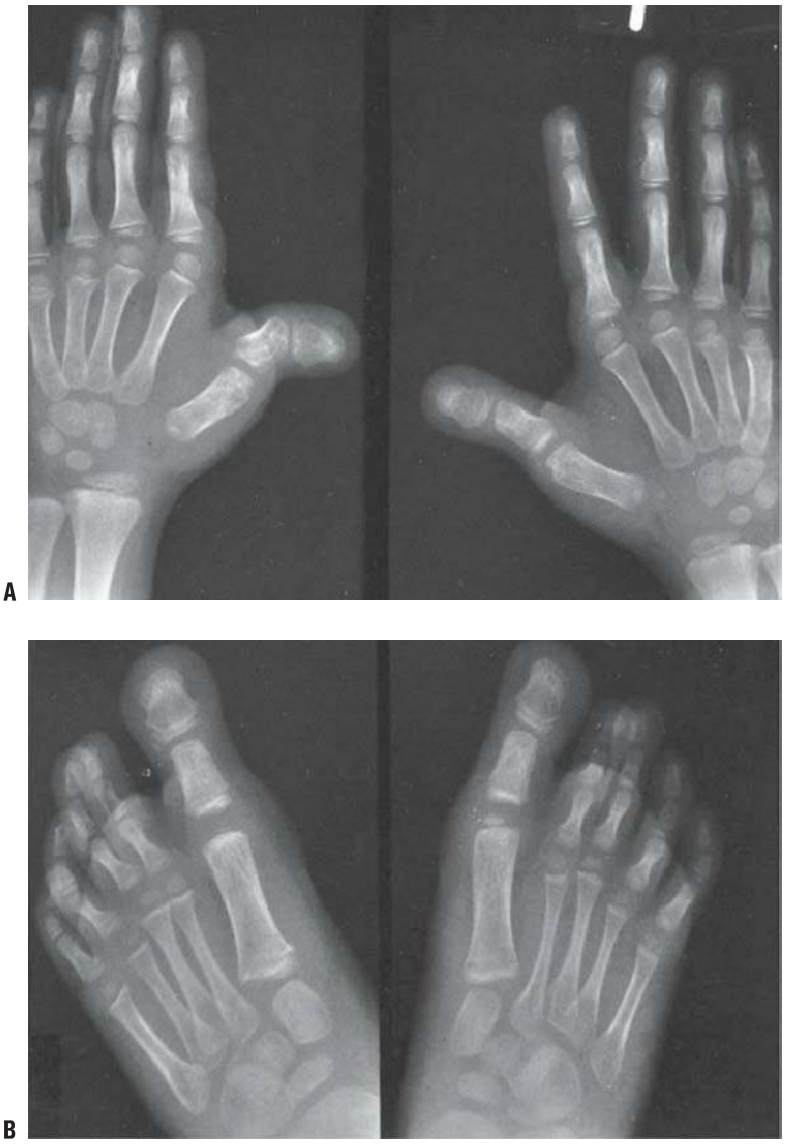


FIGURE 8-34. Rubinstein-Taybi syndrome in a 7-year-old patient. **A:** The thumbs are malformed, with a trapezoid proximal phalanx. The epiphysis extends around the radial side. **B:** The feet are more symmetric. Notice the broadening of the distal phalanx of the great toe. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

medical problems include visual disturbances, congenital heart disease, and gastrointestinal abnormalities. Later in life, frequent upper respiratory infections are related to abnormal craniofacial features, severe dental caries are common, and other infections lead to morbidity (363–365). Individuals with this syndrome are predisposed to certain types of central nervous system and head and neck tumors (366).

The thumb is treated if the radial deviation interferes with pinch, in which case osteotomy of the proximal phalanx should be performed. The deformity is progressive, and recurrence is common, as with any delta phalanx. The toe rarely requires treatment unless there is a significant congenital hallux varus. Patellar dislocation occurs in this syndrome. Although reports suggest that early surgical intervention might improve function, there are no data comparing early surgical treatment with other managements to support this concept. If surgery is performed, the addition of an extensive quadriceps mobilization seems to decrease the revision rate (367, 368). We reserve surgical intervention for the patella dislocation for symptomatic cases, or for cases in which the dislocation is clearly interfering with a patient's ability to function. There can be cervical spinal abnormalities, including upper cervical instability and stenosis (322). The mental retardation may mask underlying neurologic problems related to the cervical spine, or to other conditions, such as a tethered cord (323).

Approximately one-third of patients have structural or conductive heart defects. Patients are sensitive to many anesthesia drugs, including neuromuscular blocking agents, which tend to induce arrhythmias and prolong awakening from anesthesia (369, 370). Keloid formation is common (371).

PROTEIN PROCESSING GENES (ENZYMES)

Enzymes modify molecules or other proteins. They often modify substances for degradation, and cause cell dysfunction when mutated because of the accumulation of these substances. Mutations in genes that encode for enzymes can have a wide variety of effects on cells, resulting in a broad range of abnormalities in cell function and a wide range of clinical

findings. Many of these disorders result in the excess accumulation of proteins in cells. In these cases, the cells become larger than normal. This results in increased pressure in bones, causing avascular necrosis, and in increased extradural material in the spine, potentially causing paralysis. Multiple systems are almost always involved in these disorders. Medical treatments to replace the defective enzyme have been developed for many of these disorders, and such treatments will often arrest, but not reverse, the skeletal manifestations of the disorder. Early diagnosis and appropriate medical treatment are slowly decreasing the number of these individuals who present to orthopaedists with musculoskeletal problems. Most enzyme disorders are inherited in an autosomal recessive manner.

Mucopolysaccharidoses. This group of genetic disorders is characterized by excretion of mucopolysaccharide in the urine (372). There are at least 13 types (Table 8-4). The mild-to-severe mucopolysaccharidoses (MPS) have similar radiographs and different clinical features, but each produces a particular sugar in the urine because of a specific enzyme defect (372, 373). Changes in the naming and numbering of systems over the years have introduced considerable confusion in understanding the MPS. The incidence is 1 in 10,000.

The patients have somewhat thickened and coarse facial features and short stature, and many develop stiff joints (Fig. 8-35), especially in the hands. Stiffness is postulated to be the result of the deposition of mucopolysaccharide in the capsule and periarticular structures, and is thought to reflect the loss of joint congruity. Radiographs reveal oval vertebral

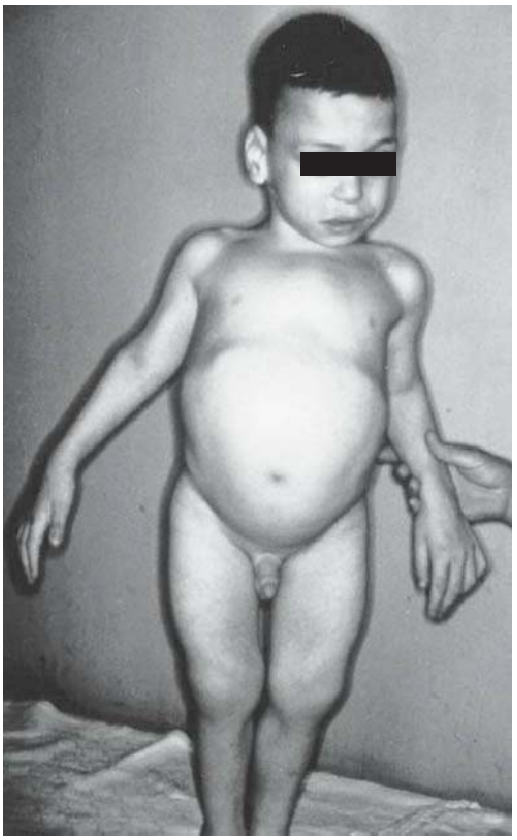


FIGURE 8-35. The classic appearance of a mucopolysaccharidosis in a 3-year-old patient includes facial features that are mildly coarsened, an abdominal protuberance from an enlarged spleen and liver, a short trunk, and stiff interphalangeal joints of the fingers.

TABLE 8-4 Mucopolysaccharidoses

Designation	Name	Enzyme Defect	Stored Substance	Inheritance Pattern
MPS I	Hurler/Scheie	α-L-iduronidase	HS + DS	Autosomal recessive
MPS II	Hunter	Iduronidase-2-sulfatase	HS + DS	X-linked recessive
MPS IIIA	Sanfilippo A	Heparin-sulfatase (sulfamidase)	HS	Autosomal recessive
MPS IIIB	Sanfilippo B	α-*N*-acetylglucosamidase	HS	Autosomal recessive
MPS IIIC	Sanfilippo C	Acetyl-CoA: α-glucosaminide-*N*-acetyltransferase	HS	Autosomal recessive
MPS IIID	Sanfilippo D	Glucosamine-6-sulfatase	HS	Autosomal recessive
MPS IVA	Morquio A	*N*-acetyl galactosamine-6-sulfate sulfatase	KS, CS	Autosomal recessive
MPS IVB	Morquio B	β-D-galactosidase	KS	Autosomal recessive
MPS IVC	Morquio C	Unknown	KS	Autosomal recessive
MPS V	Formerly Scheie disease, no longer used			
MPS VI	Maroteaux-Lamy	Arylsulfatase B, *N*-acetylgalactosamine-4-sulfatase	DS, CS	Autosomal recessive
MPS VII	Sly	β-D-glucuronidase	CS, HS, DS	Autosomal recessive
MPS VIII		Glucosamine-6-sulfatase	CS, HS	Autosomal recessive

MPS, mucopolysaccharidoses; HS, heparan sulfate; DS, dermatan sulfate; KS, keratin sulfate; CS, chondroitin sulfate.

bodies that are often beaked anteriorly; a pelvis with wide, flat ilia; capacious acetabuli; unossified femoral head cartilage; and coxa valga. The radiographic and clinical features are usually not apparent at birth, but become more apparent as the child gets older. Thus, it may be difficult to diagnose a mucopolysaccharidosis during the first year of life.

All the MPS are autosomal recessive except for mucopolysaccharidosis type II (Hunter syndrome), which is X-linked. The most common MPS are type I (Hurler syndrome) and type IV (Morquio syndrome).

The MPS can be diagnosed by urine screening, using a toluidine blue-spot test. If the initial results are positive, specific blood testing is done for the associated sugar abnormality. Although spot tests are quick and inexpensive, they have high false-positive and high false-negative rates. They are the initial tests that are often obtained before molecular genetic analyses.

The pathobiologic mechanisms are similar for all the MPS. Each has a deficiency of a specific lysosomal enzyme that degrades the sulfated glycosamine glycans: heparan sulfate, dermatan sulfate, keratan sulfate, and chondroitin sulfate. The incomplete degradation product accumulates in the lysozymes themselves. The MPS are part of a larger group of disorders known as the *lysosomal storage diseases*. The incomplete product accumulates in the tissues such as the brain, the viscera, and the joints. This unremitting process leads to the clinical progression of the disease. The child is normal at birth, but a problem may be chemically detectable by 6 to 12 months of age, and clinical progression is apparent by 2 years of age. This accumulation is responsible for the development of avascular necrosis, presumably because of too much material in the intramedullary space, and also contributes to spinal cord compressive symptoms, because of accumulation of material in the spinal canal.

Mucopolysaccharidosis Type I. MPS type I is the clinical prototype. It is characterized by a deficiency of L-iduronidase, the enzyme that degrades dermatan sulfate and heparan sulfate. The Hurler and Scheie forms represent the severe and mild ends of the clinical spectrum in MPS I. Children with the Hurler form have progressive mental retardation, severe, multiple skeletal deformities, and considerable organ and soft-tissue deformities, and die before the age of 10 years. The Scheie form is characterized by stiffness of the joints and corneal clouding, but no mental retardation; the diagnosis is usually made at approximately 15 years of age, and the patient has a normal life expectancy. Many patients with MPS I fall in the middle of this clinical spectrum. The clinical variation is determined by the location and the type of mutation that occurs along the gene for L-iduronidase (374, 375).

Marrow transplantation is used in the treatment of the more severe forms (Hurler syndrome). However, the results on the bones are variable (376), with most children still developing the typical skeletal phenotypic features despite undergoing successful bone marrow transplant (377, 378). This may be due to the poor penetration of the enzyme derived from the transplanted leukocytes to the osseous cells or to other not completely understood functions of the protein in osteoblasts and chondrocytes (305, 376). There is an initial improvement, or at least an arrest in progression of the nonosseous neurologic manifestations of the disease with marrow transplant. Some longer term studies cast doubt on the long-term effectiveness of marrow transplantation (379). Despite these disappointing longer term reports, marrow transplant may provide short-term improvement, especially in the nonosseous manifestations, and children treated with bone marrow transplantation have a good ambulatory ability (307). It also may be that earlier marrow transplantation will result in better neural function. The musculoskeletal deformities that persist after marrow transplant still require treatment (335).

Malalignment of the limbs can occur, and guided growth techniques, or osteotomies, may be necessary for genu valgum (380). Osteotomies may be associated with recurrence, and as such guided growth approaches are an attractive alternative, however, comparative series are lacking in the literature. Approximately one-fourth of the patients have an abnormality of the upper cervical spine. Odontoid hypoplasia and a soft-tissue mass in the canal can be managed like those in Morquio syndrome (described in the following text). The accumulation of degradation products in closed anatomic spaces, such as the carpal tunnel, causes "triggering" of the fingers and the carpal tunnel syndrome. These can be managed operatively (381, 382).

Mucopolysaccharidosis Type IV. Between 1929 and 1959, there was a miscellany of skeletal diseases described as *Morquio syndrome*, including several types of spondyloepiphyseal dysplasia. Morquio syndrome is an autosomal recessive disorder with an incidence of 3 per 1,000,000 of the population. Three types of Morquio syndrome are classified as subtypes of MPS IV. All are caused by enzyme defects involved in the degradation of keratan sulfate (372–374).

Patients with severe classic MPS IVA are short-trunked dwarfs, although they appear normal at birth. They develop corneal opacities. The bone dysplasia is radiographically obvious, and the final height is <125 cm (50 in.). Patients have abnormal dentition. The deficient enzyme is *N*-acetylgalactosamine-6-sulfate sulfatase, and the chromosomal defect occurs at 16q24.3 (383). Patients with intermediate MPS IVB have the same but milder phenotypes as those with type IVA. They are taller, with final heights >125 cm (50 in.), and they have normal dentition. Here, the enzyme defect is β-D-galactosidase. Patients with mild MPS IVC have very mild clinical manifestations.

The three forms of Morquio MPS IV can be distinguished by the severity of symptoms and the patient's age at detection. All these patients are normal at birth. For patients with the severe type IVA, the diagnosis is made between 1 and 3 years of age; those with the mild type IVC are diagnosed as teens, and those with the intermediate form (type IVB) are diagnosed

somewhere in the middle of this age range. The three forms may also be separated by the severity of the radiographic changes.

Intelligence is normal in patients of all of the MPS IV types, and only rarely are the facial features coarsened. Similarly, all are short-trunked dwarfs with ligamentous laxity; the laxity is rather profound in MPS IVA. The degree of genu valgus is significant, aggravated by the lax ligaments (384–387).

Management of the knee proves difficult because of the osseous malalignment and the lax ligaments. Although it is observed that the fingers and joints are becoming stiff, the medial and lateral instability of the knee remains. Realignment osteotomies can restore plumb alignment, but recurrence may occur, and osteomies may not control the instability during ambulation. The prophylactic use of braces to prevent initial valgus or recurrent deformity after surgery has not been effective (384–387). Guided growth is an attractive alternative to osteomies, avoiding issues of recurrence, but comparative studies are lacking. The hips and knees develop early arthritis. The hips show a progressive acetabular dysplasia. Radiographs may show a small femoral ossific nucleus, but an MRI or arthrogram will show a much larger cartilaginous femoral head. The femoral capital epiphyses are initially advanced for the patient's age, but between 4 and 9 years of age, the femoral heads grow smaller and then disappear altogether (Fig. 8-36). The pathophysiology of the progressive hip disease is not completely understood, and neither medication nor surgery has been shown to improve the prognosis (384–387). Patients may require total joint replacement surgery (388).

Odontoid hypoplasia or aplasia is common, with resultant C1–C2 instability (389–392) (Fig. 8-36). There is a soft-tissue mass in the spinal canal, contributing to cord compression (393, 394). This soft-tissue mass can make the space available for the cord smaller than one would expect on the basis of radiographs alone. Neurologic function, especially upper extremity strength and tone, is probably more important than measuring distances on dynamic cervical spine films. The upper and lower extremity findings are often of flaccidity rather than spasticity. The onset of the myelopathy can occur as early as the first decade of life, progressing as the soft-tissue hypertrophies, with the C1–C2 instabilities aggravating the situation. Sudden deaths of patients with Morquio disease have been reported, and they are typically attributed to the C1–C2 subluxation. C1–C2 fusion before the onset of symptoms is controversial, but promoted by some (393, 395). Others think the best surgery is occipital cervical fusion because it reduces the anterior soft-tissue mass (394, 395). There are no comparative studies evaluating the outcomes of each of the different management approaches. On the basis of the available information, it is reasonable to obtain MRI studies on symptomatic individuals, or on those with radiographic evidence of instability. C1–C2 fusions are recommended for asymptomatic individuals with MRI evidence of cord compression. Symptomatic individuals should have fusions throughout the region of instability and cord compression. Although decompression is usually performed along with the fusion, anecdotal evidence suggests that fusion alone may be sufficient, resulting in the soft-tissue mass decreasing in size.

Elsewhere in the spine, the vertebrae show a progressive platyspondylia with a thoracic kyphosis. Progressive deformity should be surgically stabilized. Anterior instrumentation is an effective surgical technique (396). Despite these problems, many patients with Morquio disease live for decades. Cardiorespiratory disease is common, but the problems at the upper cervical spine account for most disabilities.

SYNDROMES OF UNKNOWN ETIOLOGY

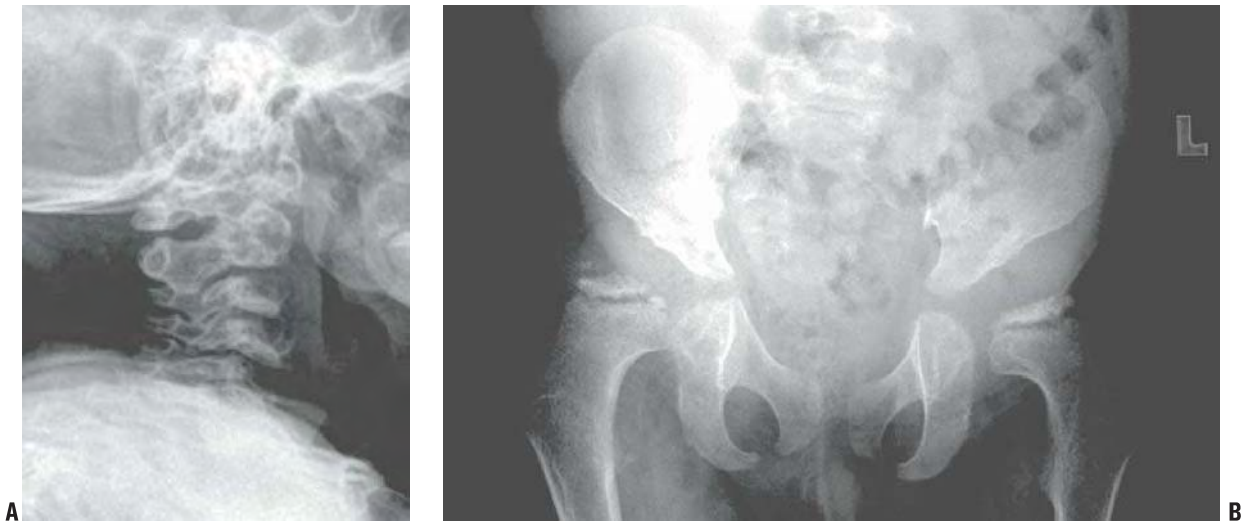
Hadju-Cheney Syndrome. Hadju-Cheney syndrome, also called *arthrodentosteodysplasia*, consists of acroosteolysis, with osteoporosis and hypoplastic changes in the skull and the mandible. The osteoporosis leads to multiple fractures of the skull, spine, and digits. The cranial sutures persist; wormian bones are seen on the skull radiographs. Basilar impression is a common finding, often requiring operative intervention. The terminal digits exhibit gradual loss of bone mass, sometimes called *pseudoosteolysis*. Patients tend to have deep voices (397–401).

Orthopaedic manifestations include loose-jointedness, patellar dislocations, scoliosis, frequent fractures, and basilar impression (402). The basilar invagination can cause hydrocephalus and an Arnold-Chiari malformation (403). This is usually managed by decompression and an occiput-to-upper-cervical-spine fusion (Fig. 8-37). Not much data are available on the management of other musculoskeletal problems. Scoliosis can be managed as in idiopathic scoliosis, although the underlying osteopenia and associated spinal fractures may make nonoperative management more difficult. The use of bisphosphonate therapy to treat the osteopenia has been reported (404), although it is not known whether this therapy will improve the clinical outcome for children with this disorder.

Polycystic kidney disease and cardiac valvular disease are reported in some Haju-Cheney patients, and thus cardiac and renal functions should be evaluated before placing the patients under anesthesia (405, 406). The disorder can be inherited in an autosomal dominant manner, but the causative gene is unknown.

Progeria. Progeria (Hutchinson-Gilford syndrome) is the best known of many syndromes characterized by premature aging. It is exceedingly rare, with fewer than 30 affected children in North America. The cause is entirely unknown. Autosomal dominant (407) and autosomal recessive (408) inheritance patterns have been proposed, but a sporadic mutation is more likely (409).

These individuals have low levels of growth hormones, and hormone supplementation will increase growth velocity, but not result in improved survival (410). The cause of the



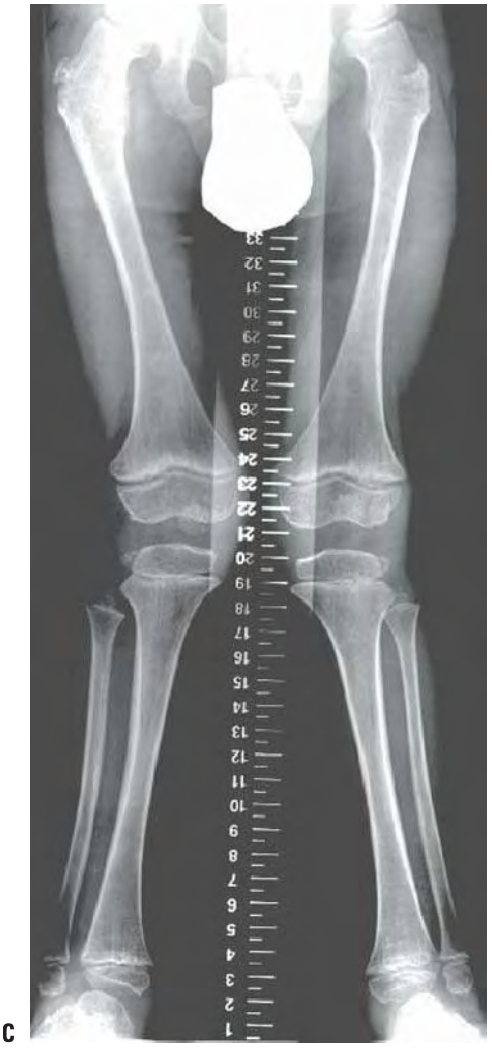
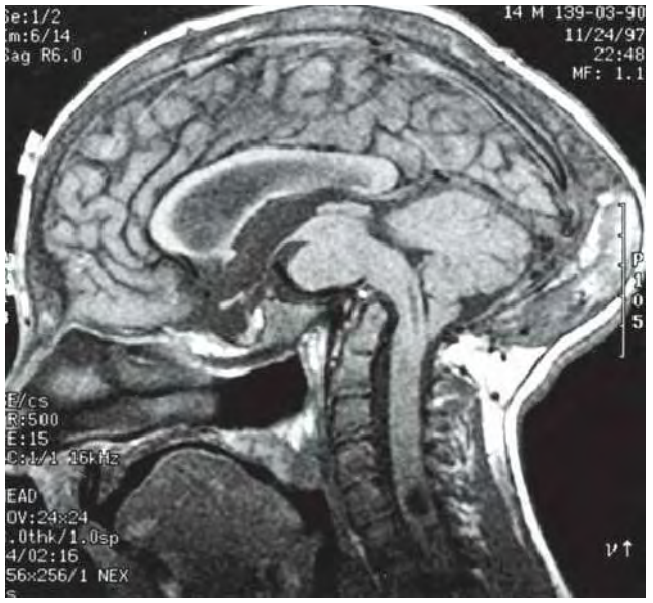


FIGURE 8-36. Morquio syndrome. The radiographic features include an absent odontoid **(A)**, a pelvis with capacious acetabuli and coxa valga **(B)**, and marked platyspondyly **(C)**. It is difficult to imagine that these vertebrae were normal at birth. Genu varum is common.

condition is not known, but a number of reports refer to the use of tissues from these patients in studying the aging process. Fibroblasts from tissue cultures derived from these individuals show a variety of abnormalities, including a decreased ability to clear free radicals (411).

Children with progeria are diagnosed between 1 and 2 years of age by their clinical features alone. There is severe growth retardation and an inability to gain weight. If there is survival to adolescence, there is no pubertal growth spurt. Alopecia and a loss of subcutaneous fat are dramatic, and



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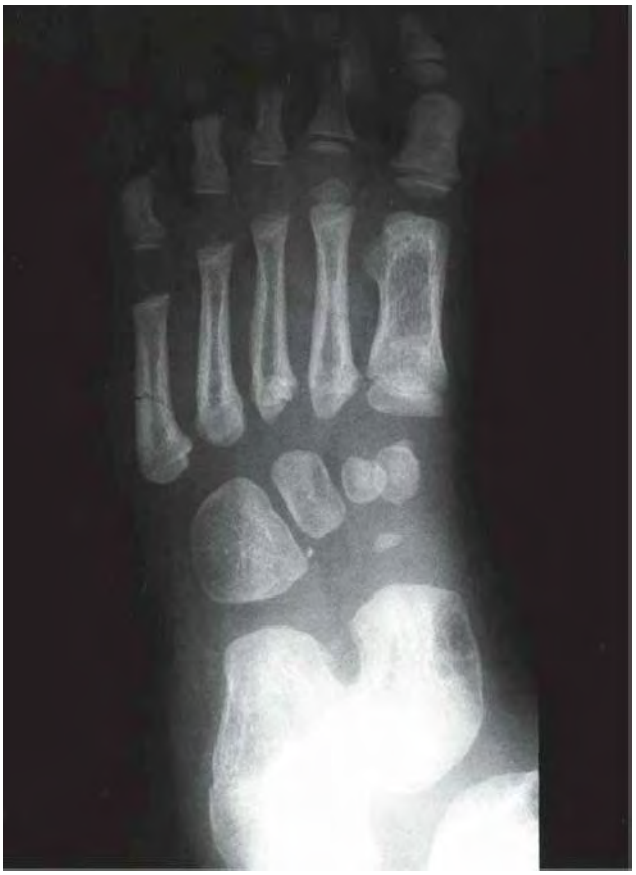

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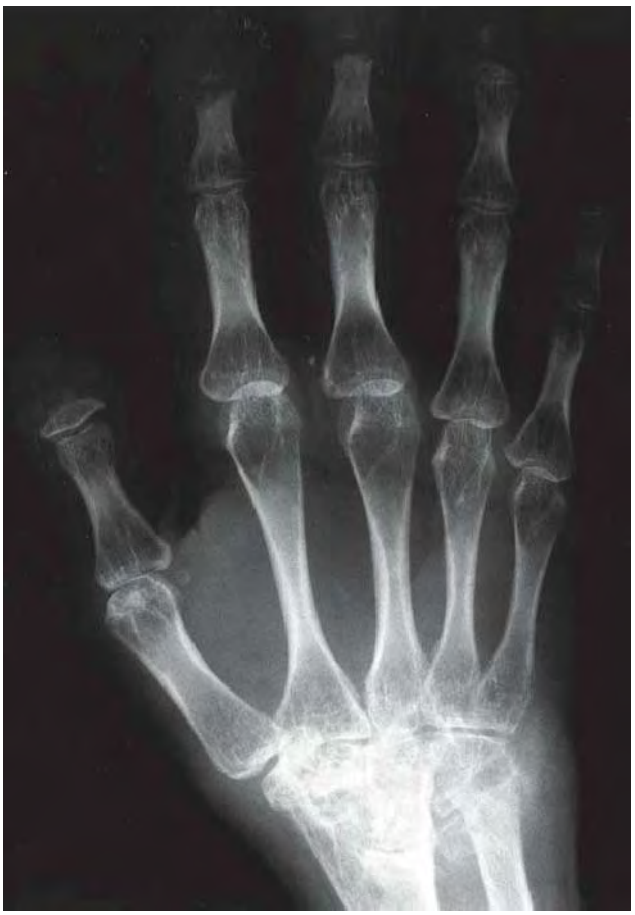

C

FIGURE 8-37. Hadju-Cheney syndrome. **A:** MRI of the head shows marked basilar invagination with an associated syrinx in the cervical cord. **B:** Radiographs show osteoporosis with pathologic fractures. **C:** Loss of bone mass in the terminal digits, termed *pseudoosteolysis*.

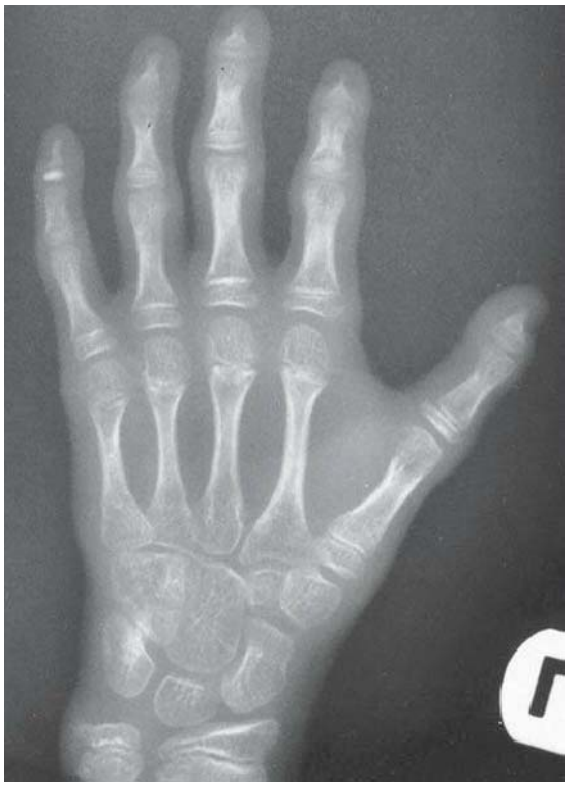

FIGURE 8-38. Progeria. The radiograph shows distal acrolysis, with resorption of the distal phalanges. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

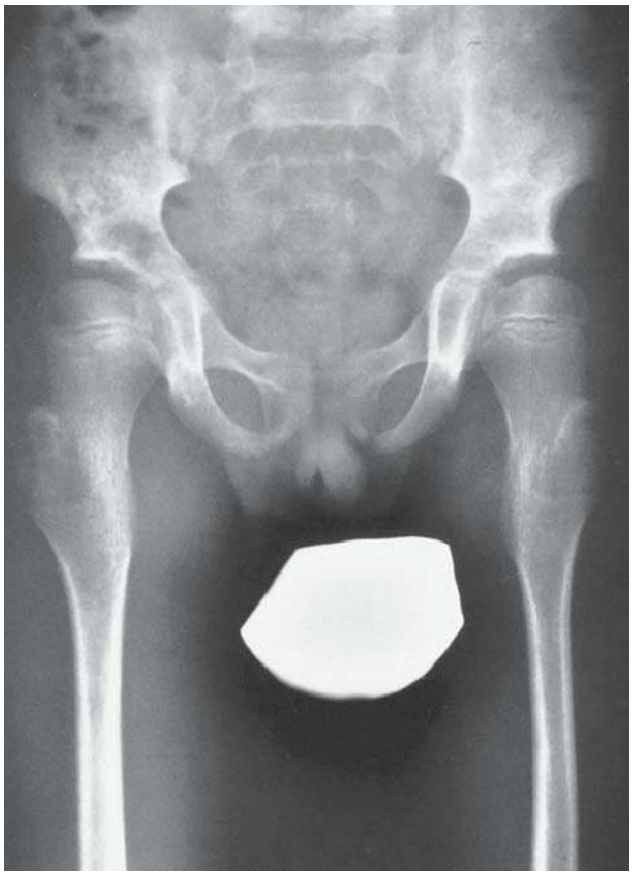

FIGURE 8-39. Progeria in an 11-year-old patient. The radiograph shows a marked degree of coxa valgus and some femoral head uncovering.

account for the distinctive appearance of a skinny old man or woman (412, 413). These patients have stiffness of the joints that is not arthritis, but a periarticular fibrosis. Osteolysis occurs in the fingertips, clavicle, and proximal humerus (407, 414, 415) (Fig. 8-38). The vertebrae may become osteopenic, creating fish-mouth vertebral bodies on radiographs (416–418). Fractures are common, often with delayed union. There is late developmental dysplasia of the hip, and the onset of a rather significant coxa valga (419, 420) (Fig. 8-39). The children do not live long enough to develop arthritis secondary to the acetabular dysplasia. Not all systems age. There are no cataracts; there is no senility. Rather than actually aging, the normal tissues undergo an atrophic or a degenerative change that mimics normal aging. The principal histopathologic atrophic changes occur in the skin, subcutaneous tissue, bone, and cardiovascular system. Atherosclerosis with myocardial infarction by 10 years of age is the rule, and life expectancy rarely exceeds 20 years.

The children show vitality until they are struck down by myocardial infarction. Despite a short life, it is imperative not to permit any suffering. Hip surgery is indicated only if there is a documented functional impairment. Surgery is not indicated to prevent future arthritis. There is no medical treatment for the basic disease process.

CONTRACTURE SYNDROMES

Although contractures are a common feature in a variety of orthopaedic conditions ranging from neuromuscular disorders to the sequelae of injury, there are several disorders in which contractures are the most prominent phenotypic feature. These syndromes are caused by a wide variety of etiologies, including mutations causing developmental problems, mutations dysregulating muscle function, and fetal environmental causes. Many of these are associated with problems in muscle function, as in the case of distal arthrogryposis, which is caused by mutations disrupting fast-twitch muscle fiber activity; there is some overlap in phenotype between these conditions and some of the myopathies. There are many such disorders of different etiologies but, because the management for many of these disorders follows similar guidelines, they are considered together in this chapter.

Arthrogryposis. Arthrogryposis is really a physical finding, not a diagnosis, and represents a large group of disorders, all of which include contractures of joints present at birth. The contracted joints lack skin creases. Since joint creases develop in the intrauterine environment, this clinical finding indicates that a congenital etiology to the contracture. *Arthrogryposis* is used as a noun to describe specific diseases, and as an adjective,

arthrogrypotic to refer to rigid joint contractures. There are at close to 100 distinct syndromes coded under the term *arthrogryposis* in the OMIM (5), illustrating the large variety of etiologies associated with this term. Most of the syndromes have different clinical courses, prognoses, genetics, causes, and pathologic processes, often making it difficult for the orthopaedist to determine the management of an individual patient (421, 422). A simple way to think about these disorders is to consider them as contracture syndromes, which can be grouped into a few general categories, each of which can be represented by a prototypic disease.

Contracture syndrome groups:

1. Involving all four extremities. This includes arthrogryposis multiplex congenita and Larsen syndrome, with more or less total body involvement.
2. Predominantly or exclusively involving the hands and feet. These are the distal arthrogryposes. Facial involvement can occur with some of these syndromes, and Freeman-Sheldon whistling face is included.
3. Pterygia syndromes in which identifiable skin webs cross the flexion aspects of the knees, elbows, and other joints. Multiple pterygias and popliteal pterygia fit into this group.

Contracture Syndromes Involving All Four Extremities

Arthrogryposis Multiplex Congenita. Arthrogryposis multiplex congenita is the best known of the multiple congenital contracture syndromes (423, 424). Although attempts have been made to change the name *arthrogryposis multiplex congenita* to *multiple congenital contractures* or *amyoplasia* (AMP), the popularity of *arthrogryposis* remains.

The etiology of arthrogryposis multiplex congenita is unknown. It was initially described in 1841 by Adolf Wilhelm Otto, who referred to his patient as a "human wonder with curved limbs" (425). The disorder is sporadic, with affected individuals having reproduced only normal children. Classic arthrogryposis can affect only one of identical twins (426, 427). The development of arthrogryposis may be influenced by an adverse intrauterine factor or the twinning process itself. Teratogens have been suggested, but none are proven, despite the multiple animal models that lend support to that theory (428–432). Some mothers of children with arthrogryposis have serum antibodies that inhibit fetal acetylcholine receptor function. One possibility is that maternal antibodies to these fetal antigens cause the disorder (433).

Histologic analysis discloses a small muscle mass with fibrosis and fat between the muscle fibers. Myopathic and neuropathic features are often found in the same muscle biopsy specimen. The periarticular soft-tissue structures are fibrotic and, in essence, there is a fibrous ankylosis. The number of anterior horn cells in the spinal cord is decreased, without an increase in the number of microglial cells (434–436). The pattern of motor neuron loss in specific spinal cord segments correlates with the peripheral deformities and the affected muscles, suggesting that a primary central nervous system disorder plays an important role in causing this condition (437).

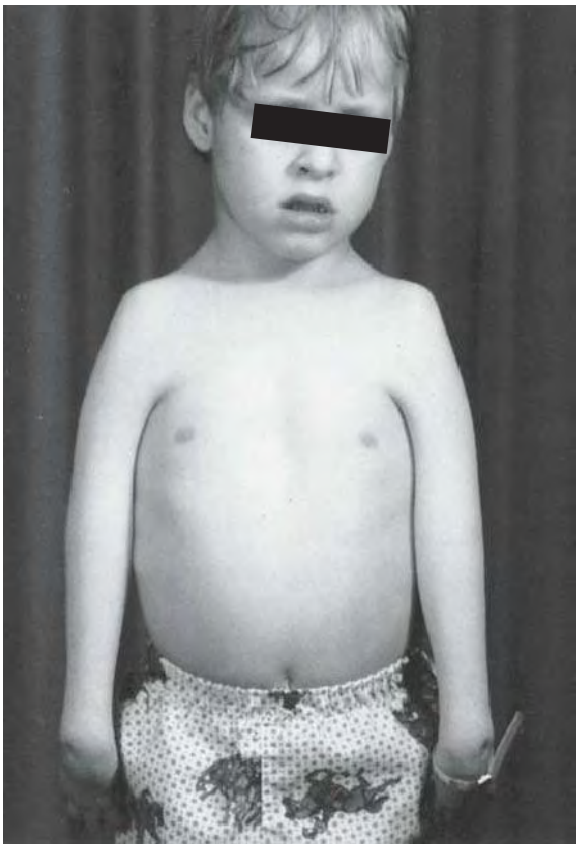

FIGURE 8-40. Arthrogryposis multiplex congenita. The picture shows the classic limb position and fusiform limbs lacking flexion creases.

Clinical examination remains the best way to establish a diagnosis. The limbs are striking in appearance and position (Fig. 8-40). They are featureless and tubular. Normal skin creases are lacking, but there may be deep dimples over the joints. Muscle mass is reduced, although in infancy there is often abundant subcutaneous tissue. Typically, the shoulders are adducted and internally rotated, the elbow more often extended than flexed, and the wrist flexed severely, with ulnar deviation. The fingers are flexed, clutching the thumb. In the lower extremities, the hips are flexed, abducted, and externally rotated; the knees are typically in extension, although flexion is possible; clubfeet are the rule. Motion of the joints is restricted. The condition is pain-free, with a firm, inelastic block to movement beyond a very limited range. In two-thirds of the patients, all four limbs are affected equally, but in one-third, lower limb deformities predominate. Only on rare occasions do the upper extremities predominate. Deformities tend to be more severe and more rigid distally. The hips may be dislocated unilaterally or bilaterally.

The viscera are usually spared from malformations, although gastroschisis has been reported. As a consequence of the general muscle weakness, there is a 15% incidence of inguinal hernia. Major feeding difficulties, caused by a stiff jaw and an immobile tongue, are frequently encountered in infancy, and lead to respiratory infections and failure to thrive (389). The face is not particularly dysmorphic. A few subtle

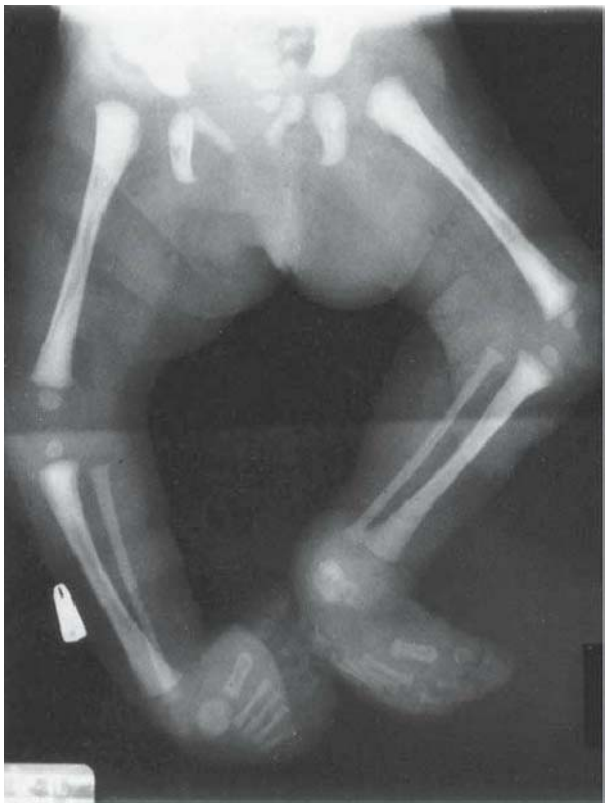

FIGURE 8-41. Arthrogryposis multiplex congenita at birth. Features include clubfeet, knee-flexion deformity, and dislocated right hip. The articular surfaces are normal. Adaptive changes occur as a consequence of the fixed position. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

features, such as a small jaw, narrowing of the face and, occasionally, limited upward gaze (secondary to ocular muscle involvement). A frontal midline hemangioma may help with the diagnosis (Fig. 8-40).

Radiographs early in life reveal that the joints are normal and that changes are adaptive and acquired over time as a consequence of their fixed position (Fig. 8-41) (390). There is evidence of a loss of subcutaneous fat and tissue. Electromyograms and muscle biopsies are of questionable diagnostic value. A diagnosis of arthrogryposis can be suspected when prenatal ultrasound detects an absence of fetal movement, especially if seen in combination with polyhydramnios (391).

The natural history and long-term outcomes are not well known (392, 438), although children with this condition are substantially less active than others of the same age (439). Some contractures seem to worsen with age, and the joints become stiffer. No new joints become involved. At least 25% of affected patients are nonambulatory, and many others are limited household walkers (440). As a rule, those with arthrogryposis who are very weak as infants stay weak, and those who appear stronger as infants stay strong. The dependency of adults seems to be related to education and coping skills more than to the magnitude of contractures of the joints.

Treatment. Each of the multiple joints involved presents its own unique opportunities for orthopaedic intervention, but an overview of the total patient must be borne in mind. The overall goals are lower limb alignment and stability for ambulation, and upper extremity motion for self-care (397–399, 421). Outcomes seem better if surgery on joints is done when children are younger, usually before adaptive intra-articular changes occur at ages 4 to 6. Realignment osteotomies, however, are usually performed closer to the completion of growth. Early motion, and avoidance of prolonged casting, may increase joint mobility, thereby improving function. Many children require long-term bracing or other assistive devices (424).

Contractures of the joints make the birthing process difficult, and neonatal fractures may result (400). Physical therapy should not be initiated in the newborn until such fractures are ruled out (401). Mobilization of joints may be accomplished by early and frequent range of motion exercises and splinting of the joint in a position of function with a removable orthotic (401, 424). There are no studies clearly demonstrating that early mobilization improves outcomes in these patients, but such a program may improve the passive range of motion, although the active range of motion does not improve very much (424). In our experience, early mobilization seems to be useful primarily for the upper extremities. Fractures may accompany an overly vigorous range of motion program.

Approximately two-thirds of patients have developmental dysplasia of the hip or frank dislocation (424, 441–443) (Fig. 8-41). At birth, the hips are flexed and abducted. There is considerable controversy about the management of the hips in these children. Closed reduction is rarely, if ever, successful. Operative reduction of a dislocated hip should be performed if it will improve function or decrease pain. Pain is only rarely are a problem with these hips. There is significant variability in functioning ability in these individuals because of the underlying severity of the disease, and this variability makes it difficult to determine any change in function from treating the hips. The range of motion of the hips may be important for functioning, because hip contractures, especially those that cause flexion deformity, adversely affect the gait pattern. Operative procedures to locate dislocated hips, therefore, have the potential to worsen function if they produce significant contractures (442, 444).

Studies of children with untreated dislocated hips concluded that those with bilateral dislocations frequently had satisfactory range of motion; their hips did not prevent them from walking, although rarely around the community, and pain was uncommon (441, 443, 444). Those with unilateral dislocations fared less well. More of them were limited to the household with walkers, and, although scoliosis was present in most patients, it was worse and more frequent in those with unilateral dislocations (424). In both groups, limitation of ambulation resulted more from the severe involvement of all four extremities than from the dislocated hips (424). These data, and case series suggesting little functional improvement with surgery for bilateral hip dislocations, support the concept of leaving bilaterally dislocated hips alone (424, 441, 442, 444). However, in these studies, hip surgery was delayed until the knees were mobilized,

and reductions did not occur until at least 1 year of age. This later age at reduction may be associated with higher rates of contractures and worse function. Reports of early open reduction of unilateral and bilateral dislocated hips, with a reduced period of immobilization, show improved postoperative range of motion (335, 416, 443). Hip reduction is unlikely to benefit the child who is not an ambulator; however, there is no way to comfortably predict which children will become ambulators at the age when early surgical treatment is contemplated. Longer term studies show similar results with both operative and nonoperative approaches, and a reduced range of motion in hips that have been surgically relocated. However, the numbers of patients reported in these studies were small (388). It therefore seems reasonable to perform early open reduction in most children. The exception may be a child with hips that are quite stiff. Both medial and anterior approaches are advocated for early hip reduction (445–447). More than the specific operative approach, the key factor may be to perform the hip reduction early in life, with minimal immobilization. While this may be accomplished using a medial approach, we feel that the anterior approach gives a more reliable approach in these teratologic dislocations.

Although the classic description of the knees is that they are hyperextended, most are in flexion (390, 424) (Fig. 8-41). The precise plane of motion may be difficult to determine, and although physical therapy is recommended, medial lateral instability may result. Hyperextension deformity responds better to physical therapy and splinting than do flexion deformities. If the flexion deformity remains more than 30 degrees, ambulation is difficult because of the associated relative weakness of the quadriceps in the ability to extend the knee. Sometime before 2 years of age, soft-tissue surgery, including posterior capsulotomy, and realignment of the quadriceps mechanism, should be performed. The actual procedure needs to be individualized, because each knee has a different degree of deformity. While posterior soft-tissue procedures will initially improve the range of motion and function, the contractures usually recur, along with a loss of motion (448). Soft-tissue releases may thus need to be repeated later in life, but before skeletal maturity. Distraction using an external fixator has also been reported, although even with this approach there is recurrence of the contractures (449, 450). Supracondylar osteotomies of the femur are recommended toward the end of growth to correct residual deformity (428, 451–453). Femoral shortening is a useful addition to the osteotomies, especially in cases where the neurovascular structures will be stretched by correcting the deformity. More recently, a guided growth approach at the distal femoral growth plate has been reported to correct flexion deformity of the knee although the ability of this approach to correct the quadriceps mechanism is unclear (454).

Many hyperextension deformities of the knee can be treated without surgery, but quadricepsplasty may be needed in cases with residual lack of motion. Traditional teaching advocates correction of the knee deformity before treating a dislocated hip, in order to allow stretching out of the muscles that cross both joints. However, with early operative intervention, using a short period of immobilization, the hip may be operated upon at the same time as a surgical procedure to correct a hyperextended knee deformity. In this case, the hamstring muscles are relaxed by both procedures, and the knee can be immobilized in a flexed position in the hip spica cast. A flexion deformity of the knee cannot be easily managed at the same time as hip surgery, because it is impossible to appropriately immobilize the hip with the knee held extended. Despite good initial nonoperative results in the hyperextended knee, there may be recurrence of the contracture over time, with surgery often needed later in life. An alternative technique of correction of the knee deformity is by using an external fixator, with gradual correction (448, 449); however, in most cases, an open procedure to release the contracted structures will be adequate, and the deformity may recur after treatment with gradual distraction. Late osteoarthritis seems more common in those with persistent hyperextension contracture.

A severe clubfoot is characteristic (424, 450, 454) (Fig. 8-41). Traditionally, it was felt that treatment using extensive surgery was necessary to correct the deformity; however, using the Ponseti technique with minor modifications seems to work quite well in many cases. A prolonged period of casting and a second tendo Achilles lengthening may be required (417, 455). In cases that do not respond to early manipulative therapy, circumferential releases are usually performed. While surgery for clubfoot is sometimes delayed until 1 year of age or later, as other joints, especially the knees, are attended to first, combined procedures, with minimal immobilization earlier in life, is gaining in popularity. Although primary talectomy has been recommended because of the high incidence of failed soft-tissue surgery (417, 455), most reports show good outcomes with circumferential release alone if performed before 1 year of age (456, 457), and primary talectomy should probably not be used as an initial approach. The positioning of the calcaneus is the key to achieving a good result after talectomy (457). Residual deformity in the teen years can be treated using a triple arthrodesis, or with multiple osteotomies, to maintain motion of the subtalar joints, while producing a plantigrade foot. Gradual correction using an external fixator is also possible (418), but recurrence after gradual distraction is not unusual. A vertical talus is an unusual foot deformity in arthrogryposis multiplex congenita and, if it is encountered, the physician must think of the distal arthrogryposes or pterygia syndromes.

Most patients do not require upper extremity surgical procedures. The physician should never think of an individual joint in the upper extremity but only of the whole arm (458, 459). Analysis needs to include each hand separately and also how the two hands work together as an effective functional unit; that is, a functional assessment should be made before deciding on an operation. Because of this, surgical procedures on the upper extremity are usually delayed until the children are old enough for the surgeon to make such an assessment. There are two key goals in treatment of the upper extremities: self-help skills, such as feeding and toileting; and mobility skills, such as pushing out of a chair and using crutches.

The shoulder is usually satisfactory without treatment. For the elbow, it is ideal to achieve flexion to 90 degrees from

the fixed extended position. However, when both elbows are involved, surgery to increase flexion should be done only on one side. Although the fibrotic joint capsule and the weak muscles make the prospect of achieving active elbow flexion difficult, if an extensive release with triceps lengthening is undertaken, successful improvement in the range of motion is possible (456). Passive elbow flexion to a right angle is a prerequisite for considering a tendon transfer for active elbow flexion (402). The triceps brachii and pectoralis have been the most frequently tried muscles. Success is best in children older than 4 years, and who have at least grade four strength of the muscle to be transferred (460–463). Distal humeral osteotomy, designed to place the elbow into flexion and correct some of the shoulder internal rotation deformity, may be performed toward the end of the first decade (444, 459). It is designed to improve hand-to-mouth function. Care must be taken not to externally rotate the distal humerus excessively. The hand and wrist are usually flexed and the ulna deviated, but variations within this pattern exist (403, 404). In general, the ulna-side digits are more involved. Proximal interphalangeal flexion deformities rarely respond to physical therapy or surgery. The thumb is flexed and adducted into the palm, and responds better to surgery than do the other digits.

Approximately one-third of the patients develop scoliosis (405). Curves usually have a C-shaped, neuromuscular pattern. The use of orthoses has been reported (406), although in our experience, these children respond poorly to bracing. Surgery is indicated for progressive curves interfering with balance or function. There are reports of patients regaining their ability to ambulate after surgical correction of large, rigid curves (406); surgery should be considered in patients who lose their ability to ambulate as they develop such curves.

Intelligence is normal, and these children often have a natural ability to learn substitution techniques. There is, however, a strong association between initial feeding difficulties and subsequent language development, which should not be mistaken for retardation (389).

Larsen Syndrome. The essential features of Larsen syndrome are multiple congenital dislocations of large joints, a characteristic flat face, and ligamentous laxity (407) (Fig. 8-42). The cause of the facial flattening is unclear, but it is especially noticeable when observed in profile, and is associated with some hypertelorism and a broad forehead. Dislocation of multiple joints appears in a characteristic pattern that includes bilateral dislocated knees, with the tibia anterior on the femur, bilateral dislocated hips, bilateral dislocated elbows, and bilateral clubfeet (464–468). The physician should think of this syndrome whenever dislocated knees are detected. The ligaments are lax or entirely absent. The ligamentous laxity is often so substantial that Larsen syndrome may be confused with EDS.

Radiographs show that the knees are dislocated, with the tibia anterior to the femur (408). Arthrograms show a small or an absent suprapatellar pouch, absent cruciate ligaments, and a misaligned patella (Fig. 8-43). The elbows have complex radial–humeral, ulnar–humeral, and radial–ulnar dislocations.

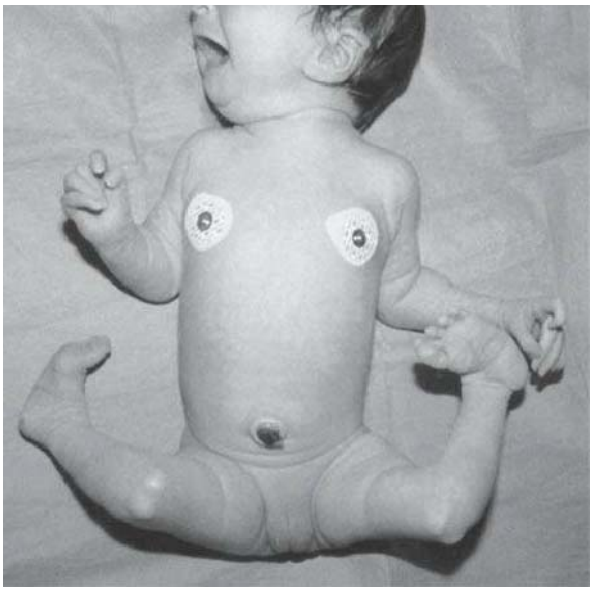

FIGURE 8-42. Larsen syndrome in a 1-week-old patient who has bilateral dislocated knees and clubfeet. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

Radial–ulnar synostosis is common and usually associated with ulnar–humeral dislocation (Fig. 8-44B). A spheroid ossicle frequently occurs anterior to the elbow joint; its origin is unknown. There are more carpal centers than are normal (Fig. 8-44A), and extra ossification centers in the foot, with a curious double ossification pattern of the calcaneus (Fig. 8-44C). This double ossification pattern can help confirm the diagnosis in cases in which the diagnosis is not clear. Abnormal cervical

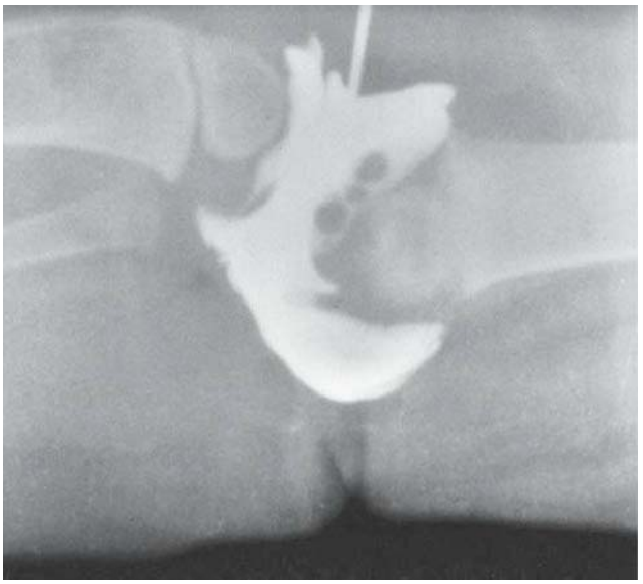

FIGURE 8-43. Larsen syndrome in a 5-month-old patient. The arthrogram of a knee shows anterior dislocation of the tibia on the femur and no suprapatellar pouch.

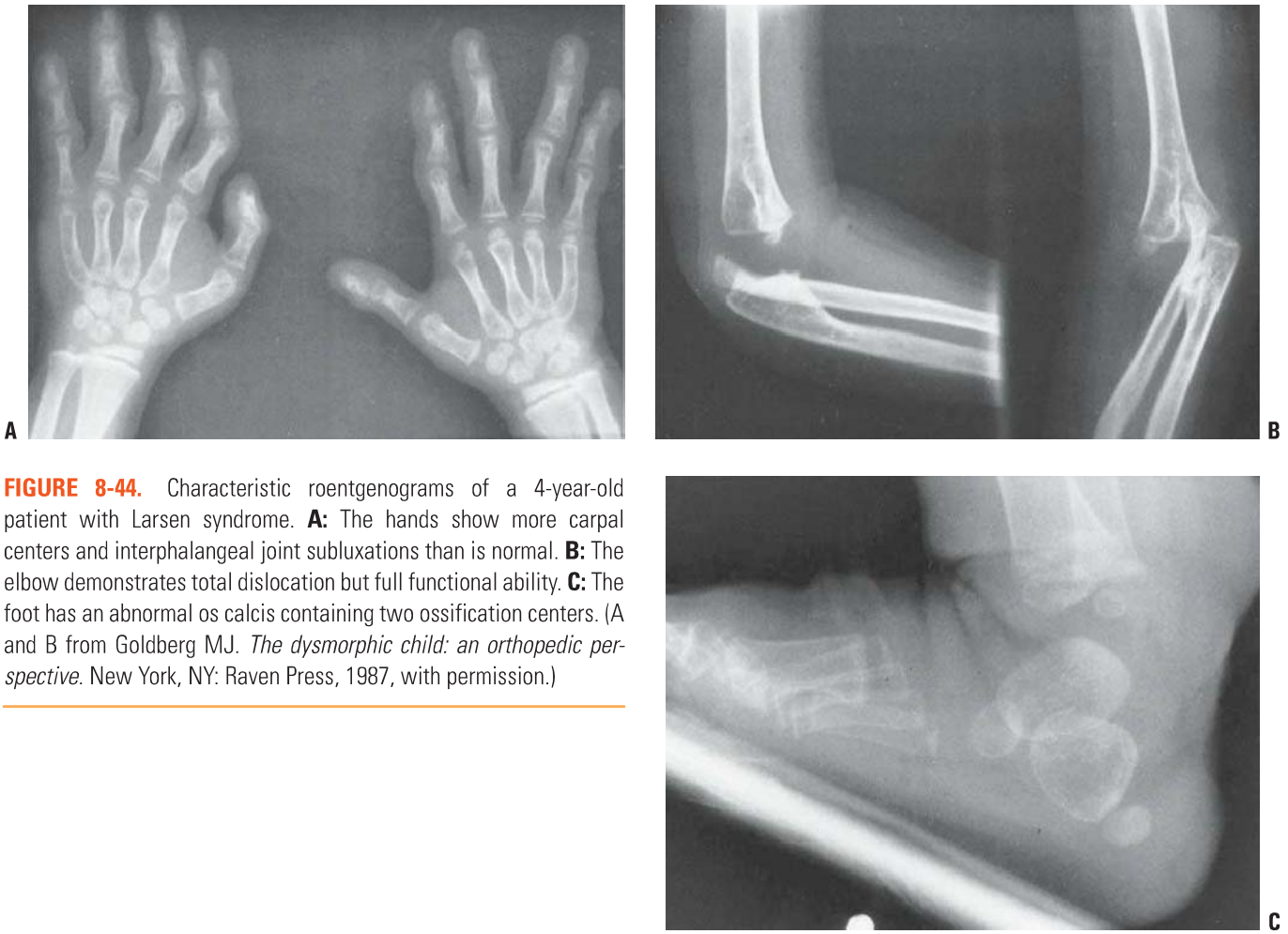

FIGURE 8-44. Characteristic roentgenograms of a 4-year-old patient with Larsen syndrome. **A:** The hands show more carpal centers and interphalangeal joint subluxations than is normal. **B:** The elbow demonstrates total dislocation but full functional ability. **C:** The foot has an abnormal os calcis containing two ossification centers. (A and B from Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

spine segmentation, with instability, is typical, as is kyphosis, a complication often associated with myelopathy. Some cases are inherited in an autosomal dominant manner, and this aids in the diagnosis.

Both autosomal dominant and recessive inheritances are reported in Larsen syndrome, although many cases are sporadic (409–411). Some autosomal dominant cases are caused by mutations in the gene encoding filamin B (412). This is an intracellular protein that serves as scaffolding on which signaling and protein trafficking pathways are organized. It is expressed in the growth plate and vertebrae, and as such, the mutation likely acts to disrupt normal patterning and development of the joints and vertebral bodies, resulting in the typical phenotypic features. Some recessive cases are due to deficiency carbohydrate sulfotransferase 3, which plays a role in glycosaminoglycan processing, also deregulating joint and spine development (457). There are cases in which only one side of the body has a Larsen syndrome phenotype, suggesting that some cases are due to somatic, or mosaic, mutations (413).

The large numbers of deformities of the lower extremities require treatment in order to achieve stable, located joints. Knee stability is important for ambulation; however, the most important factor is knee stability in extension to allow for optimal quadriceps function. The knee may remain unstable after reduction because of the lack of stabilizing ligaments, such as the anterior cruciate ligament. Long-term orthoses or anterior cruciate ligament reconstruction may be needed. Extra-articular reconstruction of the anterior cruciate ligament is another approach that maybe required (418). The knee is usually reduced before the hips, although simultaneous procedures are possible (25, 408). Although most knees do not respond to attempts at manipulation and cast correction, traditionally an initial trial of cast treatment is attempted. Too-vigorous manipulations result in distal femoral metaphyseal–physeal fractures. Because manipulation has not been found to be helpful for true dislocations, we believe that it can be abandoned once a dislocation is confirmed. Surgery may be undertaken as early as 3 to 4 months of age. Restoration of the range of motion must be cautious (gaining full extension is often a problem), and a flexion splint or a brace may be required after operative reduction to guard against redislocation.

The hips are dislocated, often despite a rather normal-appearing acetabulum. There is a sense of a good range of motion, although the hip may prove to be irreducible (414). The evolution of hip management in Larsen syndrome mirrors that in arthrogryposis multiplex congenita, and there is a trend toward earlier treatment. The relative rarity of this syndrome, however, accounts for the lack of good comparative data on

how best to manage the hip dislocations. Reduction of the hip is associated with a high redislocation rate and revision surgery (408, 414, 415). For this reason, some specialists advocate either leaving bilateral dislocated hips alone, or waiting until after 1 year of age and performing femoral and pelvic osteotomies, along with the open reduction. However, we prefer an approach similar to that in arthrogryposis, with early surgical relocation. Because the knees are hyperextended when dislocated and cast in a flexed position after surgical relocation, both knees and hips can be operated upon at the same time. Secondary osteotomy of the pelvis and femur can be performed later, if necessary.

The clubfeet can be managed in a cast until the knee deformity is corrected. Some feet can be corrected with serial casting (408). The foot may need to be braced to control ankle instability. Despite the dislocations of the elbow or shoulder, the arms remain functional and rarely require treatment. Crutches or walkers can be used despite the dislocations.

The major concern involving the spine is structural abnormalities of the cervical vertebrae (26, 419). This manifestation may occur more frequently than previously recognized, and children should have cervical spine films taken in the first year of life to identify this deformity. Kyphosis is often due to hypoplasia of the vertebral bodies. A combination of cervical kyphosis and forward subluxation may result in quadriplegia and death. Posterior stabilization early (within the first 18 months of life) may prevent the significant problems associated with treatment after myelopathy has occurred and allow for correction of a kyphotic deformity with growth (33). In more severe cases or in the face of myelopathy, anterior and posterior decompression and fusion may be required (458, 459).

Anesthesia complications are common. The mobile infolding arytenoid cartilage creates airway difficulties. The associated tracheomalacia can be especially problematic in the newborn and may delay surgery for the hips and knees (419). The anesthesiologist should be aware of possible cervical spine instability, and a preoperative lateral radiograph is recommended.

The children have normal intelligence. The prognosis is generally good with aggressive orthopaedic treatment if the child survives the first year of life. The mortality figures for the first year may be as high as 40%. During the neonatal period, the cartilage-supporting structure of the larynx and trachea is soft, and there may be alarming elasticity of the thoracic cage at the costochondral junction, leading to respiratory failure and death. Cervical spine problems may also contribute to early mortality. Congenital cardiac septal defects, elongation of the aorta, and acquired lesions of the mitral valve and aorta, similar to those found in Marfan syndrome, further complicate medical and anesthesia management (420, 421).

Contracture Syndromes Involving Predominantly the Hands and Feet

Distal Arthrogryposis. Children with distal arthrogryposis have characteristic fixed hand contractures and foot deformities, but the major large joints of the arms and legs are spared (16, 422, 423). Because different craniofacial abnormalities are often associated with distal arthrogryposis, the condition has been categorized as several eponymic syndromes (e.g., Gordon syndrome), a situation that leads to confusion (41). The cardinal features of distal arthrogryposis are the hand deformity with ulnar deviation of the fingers at the metacarpophalangeal (MCP) joint, flexion deformities at the proximal interphalangeal and MCP joints, and a cup-like palm with a single palmar crease (Fig. 8-45). The thumb is flexed and adducted, with a web at its base (424). Distal arthrogryposis is common and is sometimes incorrectly called *multiple camptodactyly*. The inheritance pattern of distal arthrogryposis is autosomal dominant, but there may be considerable variation in families, and this can lead to missing the diagnosis (41, 424–426). Distal arthrogryposis is divided into type I and type II on the basis of the absence or presence of facial findings, respectively.

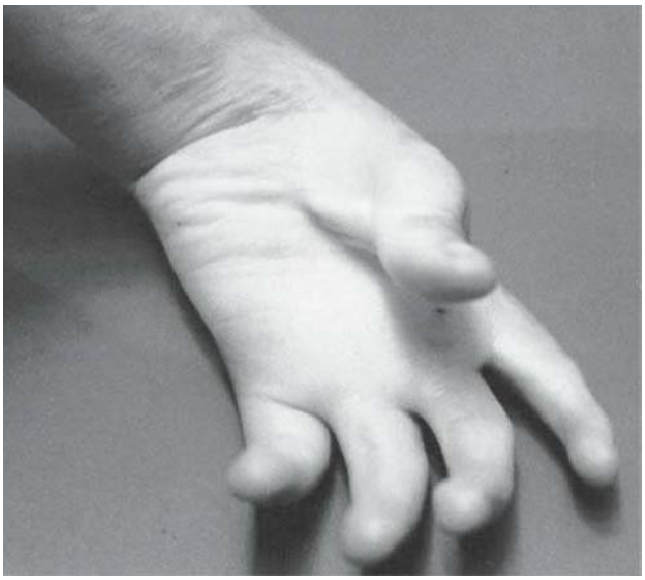

FIGURE 8-45. Distal arthrogryposis. Characteristic hand is the result of ulnar deviation at the metacarpophalangeal joints. Notice the deeply cupped palm and webbing of the MCP joint of the thumb.

Some cases of distal arthrogryposis type I are caused by mutations in the *TPM2* gene, which encodes β-tropomyosin, a protein important in fast-twitch muscle fibers (427). Type II distal arthrogryposis (Freeman-Sheldon syndrome) is caused by mutations in an isoform of troponin I that is specific to the troponin-tropomyosin complex of fast-twitch myofibers (427). Both these mutations result in abnormal activity of fast-twitch muscle fibers, suggesting that dysregulation of these muscle fibers is the common pathophysiologic cause of distal arthrogryposis. Because there are a variety of subtypes of distal arthrogryposis, it is likely that a number of causative genes will be identified, and perhaps all of these will play a role in the dysregulation of fast-twitch muscle fibers.

Although the hand deformity is characteristic and constant, the feet may be clubbed, have stiff metatarsus adductus, and have a vertical talus. The major joints in the upper

and lower extremities are otherwise normal, although a minor knee-flexion deformity may be found. Intelligence is normal. The associated craniofacial anomalies are cleft lip or cleft palate and, in such patients, the syndrome of distal arthrogryposis may have an eponymous name, such as Gordon syndrome (391, 469). Radiographs show normal bony architecture, and only with persistence of deformities in the hands and feet are articular changes detected. This syndrome can be diagnosed prenatally in the fetus by detecting an unchanged position and lack of motion of the hands in contrast to the normal activity of the large uninvolved joints (42).

Overall, children with distal arthrogryposis have good function. The hands function well because the shoulders, elbows, and wrists are normal. Thumb surgery to lengthen the flexor pollicis longus and rebalance the extensor is the most common surgery (52). The feet more frequently require surgery. Some clubfeet can be corrected with manipulation and serial casts. Most are treated with circumferential releases. The outcome of treatment of clubfoot is better in this syndrome than in other arthrogrypotic clubfeet.

Freeman-Sheldon Syndrome. Freeman-Sheldon syndrome is sometimes called *distal arthrogryposis type II* because the hand and foot deformities are similar to those of distal arthrogryposis. It is recognized by its most characteristic feature, a "whistling face" (Fig. 8-46). The original name, *craniocarpotarsal dystrophy,* is misleading because it does not involve the cranium (53, 470). This syndrome is usually sporadic, although there is evidence of autosomal dominant and autosomal recessive inheritance (428, 433, 434). The eyes are deeply set.

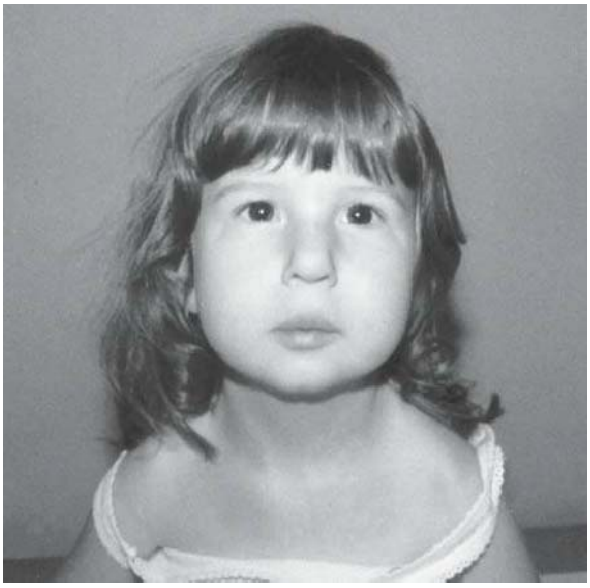

FIGURE 8-46. Freeman-Sheldon syndrome in a 3-year-old patient. Notice the small chin and mouth, long philtrum, puffy cheeks, deeply set eyes, and small chin cleft. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

The cheeks are fleshy, and pursed lips simulate whistling. There is a small mouth and a curious H-shaped dimple in the chin.

Scoliosis was not initially recognized as a common feature, but it affects more than one-half of the patients. The onset is in the first decade. It is often severe, with a left thoracic pattern reported regularly. The vertebrae are normally shaped. Although the scoliosis can be managed as in idiopathic scoliosis, the curves are more rigid and may not respond well to brace treatment (433, 435).

The hands demonstrate the classic distal arthrogryposis pattern described earlier (433, 435, 436). There are other contractures, including flexion deformities of the elbow and knee, decreased range of motion of the shoulder, decreased range of motion of the neck, and dislocated hips (77). Operative management principles for the upper extremity are similar to those in distal arthrogryposis. The hands are treated with physical and occupational therapy, but there is less improvement than is seen in the other distal arthrogryposis syndromes (437). Most of the other associated contractures can be treated like those in the other arthrogrypotic syndromes.

Clubfoot is the most common foot deformity, with vertical talus being the next most common (Fig. 8-47) (433, 435, 436). Clubfoot and vertical talus deformities are difficult to manage using manipulative techniques, but these should be tried first before using operative techniques.

During infancy, dysphagia and aspiration lead to failure to thrive, and even to death. Surgery to permit adequate mouth opening for feeding may be necessary (76). Children who survive the neonatal period do well and have normal intelligence. Anesthesia complications are common; some are the result of abnormalities related to the laryngeal cartilages (76, 389, 392, 438). The cause is unknown, but the buccinator muscle is hypoplastic, and electromyograms and muscle biopsies are identical to the peripheral muscle studies in classic arthrogryposis multiplex congenita (440), suggesting some similarity in pathophysiology.

Contracture Syndromes with Skin Webs

Pterygia Syndrome. *Pterygium* comes from a Greek word meaning *little wing*. A pterygium is a web. It can be seen as an isolated malformation in some syndromes, such as the pterygium colli in the neck of patients with Klippel-Feil syndrome.

There are two clinically important pterygia syndromes: multiple pterygium syndrome and popliteal pterygia syndrome (397). Several pterygium syndromes are lethal, with the affected patients not surviving the fetal or the newborn period (398, 471). The web syndromes are separated genetically as autosomal recessive (i.e., lethal pterygium syndrome and multiple pterygium) and autosomal dominant (i.e., popliteal pterygium) (422). However, they often overlap. Lethal pterygium syndrome may be diagnosed prenatally by detecting hydrops and cystic hygroma colli (399).

Both popliteal pterygium syndrome and van der Woude syndrome are caused by mutations in the gene encoding interferon regulatory factor-6 (400). Van der Woude syndrome is a

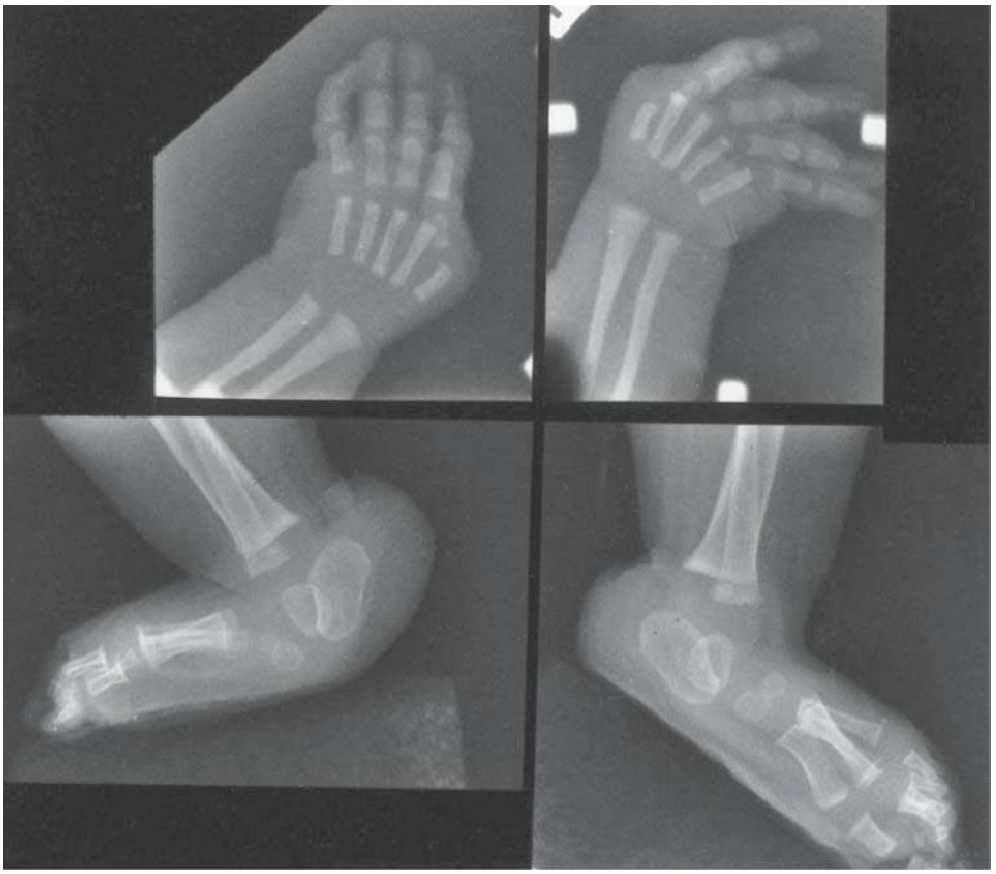

FIGURE 8-47. Freeman-Sheldon syndrome in a 5-year-old patient. Radiographs of the hands demonstrate ulnar deviation at the metacarpophalangeal joint, typical of a distal arthrogryposis syndrome. The feet show bilateral congenital vertical tali. All other joints in this patient were normal. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

dominantly inherited developmental disorder characterized by pits or sinuses of the lower lip, and cleft lip or cleft palate. It is unclear how a mutation in this interferon regulatory factor causes these seemingly dissimilar syndromes.

Multiple pterygia syndrome (i.e., Escobar syndrome) is characterized by a web across every flexion crease in the extremities, most prominently across the popliteal space, the elbow, and in the axilla (401, 441) (Fig. 8-48). There also are webs across the neck laterally and anteriorly from sternum to chin, drawing the facial features down. The fingers are webbed. The webs can be obvious, but if they are not, the affected children can look very much like those with arthrogryposis multiplex congenita. The two features that differentiate this syndrome from classic arthrogryposis are vertical talus and congenital spine deformity. The vertical talus is fairly constant in multiple pterygium syndrome and can be managed only by surgery. Circumferential release and prolonged protection, as in managing any arthrogrypotic foot deformity, are necessary. The spine deformity is significant, with multiple segmentation abnormalities and lordoscoliosis (442) (Figs. 8-49 and 8-50). The lordoscoliosis may be substantial enough to interfere with trunk and chest growth, leading to respiratory death during the first or second year of life (Fig. 8-50). Mobility depends much on the magnitude of the lower extremity webs and the residual motion of the joints, with many patients limited to wheelchairs for locomotion. The children have normal intelligence, and efforts should be maximized to enable them to function independently. Surgery is rarely needed for the upper extremities.

Popliteal pterygium syndrome (i.e., fascial-genital-popliteal syndrome) has recognizable characteristics in the face, the genitals, and the knee (75, 76, 416, 443, 444). The features include a cleft lip and palate, lip pits, and intraoral adhesions (52, 53). A fibrous band crosses the perineum and distorts the genitalia (23). A popliteal web is usually present bilaterally (76). It runs from ischium to calcaneus, resulting in a severe knee-flexion deformity. Tibia hypoplasia may be associated. Within the popliteal web is a superficial fibrous band, over which lies a tent of muscle running from the os calcis to the ischium, and is known in the older literature as a *calcaneoischiadicus muscle*. The popliteal artery and vein are usually deep, but the sciatic nerve is superficial in the web, just underneath the fibrous band (Fig. 8-51). There is a distinctive foot abnormality in this syndrome: a bifid great toenail and syndactyly of the lesser toes.

Although the original cases of multiple and popliteal pterygium syndromes were clearly defined, there is more phenotypic variation in both than was originally thought. For example, mild webs in joints of the upper extremity may be found in patients with popliteal pterygium syndrome. Adaptive changes in the joints occur over time. On radiographic examination, the patella look elongated, and the femoral condyles flattened, because of knee-flexion deformity.

From a management perspective, the determining factors are the magnitude of scoliosis and the size of the web crossing the knee. The thoracic vertebral dysplasia, thoracic lordosis, and the small chest impair lung development, resulting in

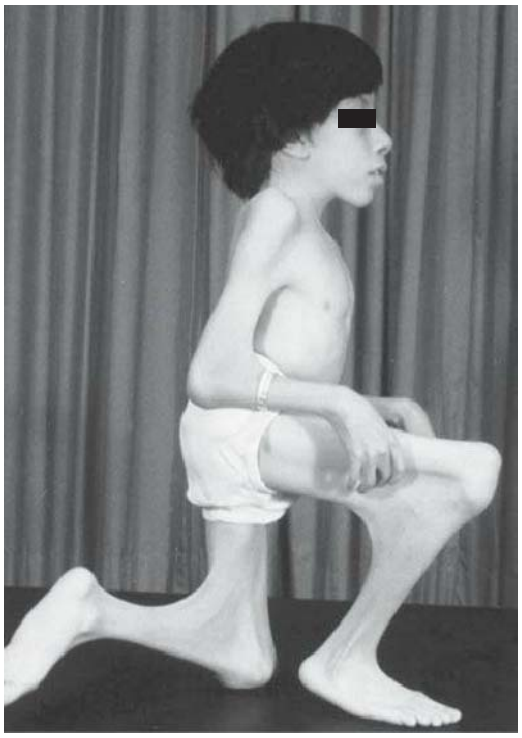

FIGURE 8-48. Multiple pterygium syndrome in a 12-year-old patient. Antecubital webs fix the elbows, and popliteal webs prevent ambulation. The patient had normal intelligence and became a college graduate. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

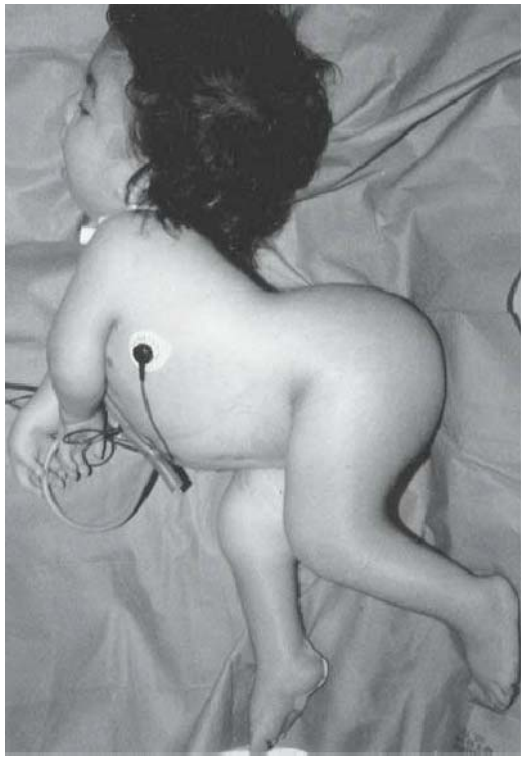

FIGURE 8-50. Multiple pterygium syndrome. Severe limitation of trunk growth was caused by vertebral fusions and lordoscoliosis. Death occurred at 24 months of age because of respiratory failure.

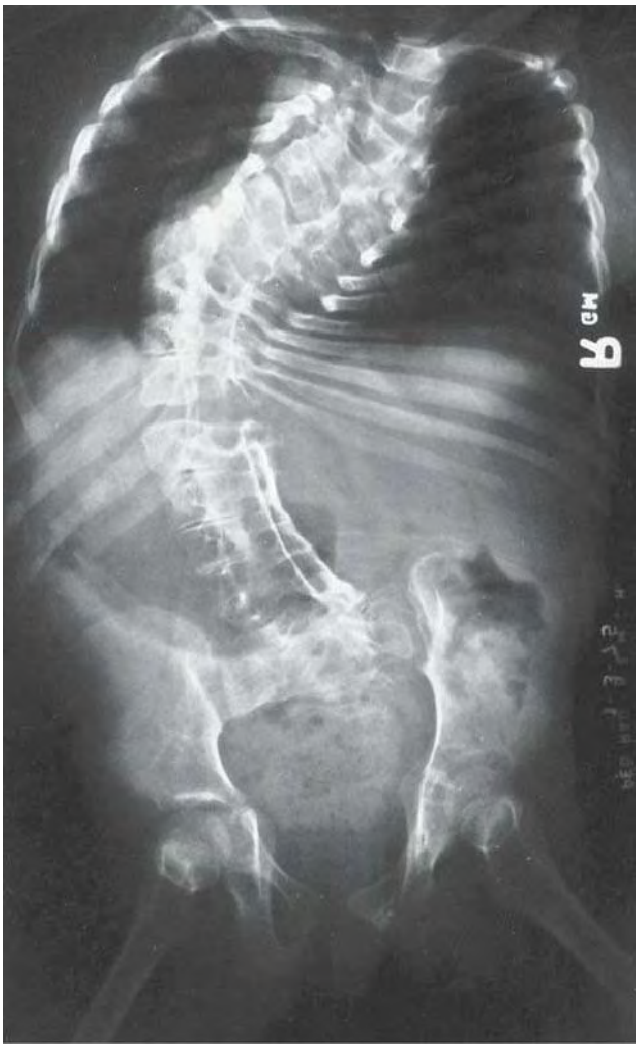

FIGURE 8-49. Multiple pterygium syndrome in a 13-year-old patient. Radiograph shows severe scoliosis, vertebral abnormalities, and an unsegmented bar from T9 to T12 and from L1 to S1, with an apparent gap between the bars. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective*. New York, NY: Raven Press, 1987, with permission.)

death in the first years of life in those with multiple pterygium syndrome. For the longer term survivors, management of the spine deformity is identical to those with nonsyndromic congenital scoliosis. Preoperative MRI evaluation of intraspinal contents and ultrasound of the kidney are indicated.

The knee is the joint that limits mobility in both syndromes and is the joint that most determines future ambulatory potential (39, 41, 42, 76). Traditionally, treatment of the knee begins with physical therapy, but the effectiveness of this therapy is doubtful. Early popliteal web surgery is recommended before the onset of adaptive changes in the articular surfaces, and before further vascular shortening. The nerve is usually located just under the skin and the web, and care must be taken to avoid nerve damage. The web is resected, and Z-plasty of the skin is performed. There is a high recurrence rate despite use of braces. Femoral shortening with an extension osteotomy is often required. If almost-full knee extension cannot be achieved at surgery, femoral shortening should

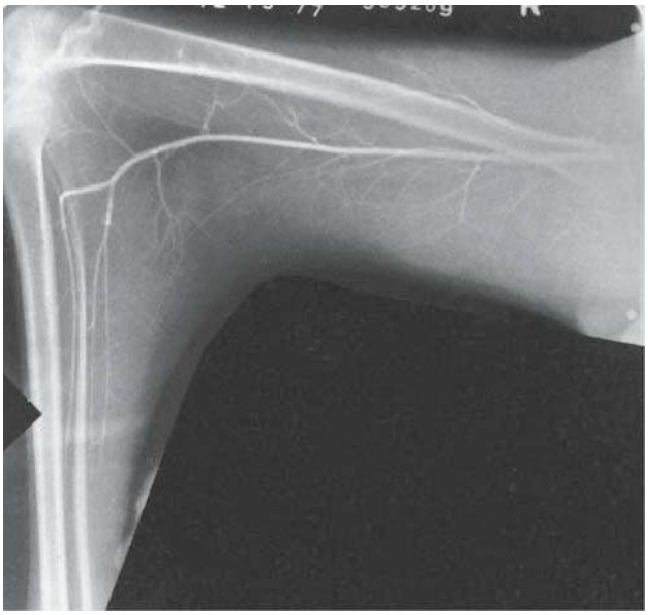

FIGURE 8-51. Popliteal pterygium in a 13-year-old patient. Arteriogram shows that the popliteal artery has been drawn up from its normal position. At the margin of the web is the sciatic nerve. (From Goldberg MJ. *The dysmorphic child: an orthopedic perspective.* New York, NY: Raven Press, 1987, with permission.)

be considered, even if during infancy or childhood (77). Gradual distraction techniques can be used, but an advantage over traditional techniques has not been demonstrated (448). Posterior soft-tissue procedures can be combined with distraction techniques to gradually extend the knee. Femoral shortening techniques are associated with low recurrence rates of the deformity, and have the advantage of reducing tension on the neurovascular structures. These techniques are therefore our treatment of choice.

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