CHAPTER 105

Heritable Diseases of Connective Tissue

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KEY POINTS

- Heritable disorders of connective tissues are a genetically diverse group of disorders and are associated with extreme variation in height, from very short individuals (dwarves) to those with tall stature.
- The osteochondrodysplasias or skeletal dysplasias are a group of more than 450 distinct disorders frequently associated with profound short stature and orthopedic complications.
- These disorders are diagnosed based on radiographic, clinical, and molecular criteria.
- There has been significant progress in elucidating the underlying molecular mechanisms in most of these disorders, providing for improved clinical diagnosis and reproductive choices for affected individuals and their families.
- Treatment options have been used in osteogenesis imperfecta, metabolic storage disorders, and Marfan syndrome, which may improve the quality of life and life span in affected individuals.

Heritable disorders of connective tissues are a heterogenous group of disorders characterized by abnormalities in skeletal tissues, which include cartilage, bone, tendon ligament, and muscle. Disorders of connective tissues have been classified based on clinical findings and molecular criteria. They are subclassified into those that primarily affect cartilage and bone, which are the skeletal dysplasias, and those that have a more profound effect on connective tissue, which include the Ehlers-Danlos syndrome, Marfan syndrome, and other disorders caused by abnormal extra-cellular matrix molecules, such as cutis laxa syndrome resulting from mutations in the gene that encodes fibulin 5.[1] The skeletal dysplasias are associated with abnormalities in the size and shape of the appendicular and axial skeleton and frequently result in disproportionate short stature. Until the early 1960s, most individuals with short stature were considered to have pituitary dwarfism, achondroplasia (short-limbed dwarfism), or Morquio disease (short-trunked dwarfism). Presently, there are more than 450 well-characterized disorders that are classified primarily on the basis of clinical, radiographic, and molecular criteria. Disorders of connective tissues are genetic in origin and result from mutations in genes that encode extra-cellular matrix proteins, transcription factors, tumor suppressors, signal transducers, enzymes, chaperones, intra-cellular binding proteins, RNA-processing molecules, ciliary proteins, and genes of unknown function.[2]

SKELETAL DYSPLASIAS

The skeletal dysplasias, or osteochondrodysplasias, are defined as disorders associated with a generalized abnormality in the skeletal. Although each skeletal dysplasia is relatively rare, collectively the birth incidence of these disorders is almost 1 in 5000.[3] These disorders range in severity from precious arthropathy to perinatal lethality caused by pulmonary insufficiency. Individuals with these disorders can have significant complications, including orthopedic, neurologic, and psychological. Many of these individuals seek medical attention for orthopedic complaints from ongoing pain, arthritic complaints in large joints, and back pain primarily caused by ongoing abnormalities in bone, cartilage, tendons, and ligaments.

Embryology

The human skeleton (from the Greek *skeletos*, dried up) is a complex organ consisting of 206 bones (126 appendicular, 74 axial, 6 ossicles). The skeleton, including tendon, ligaments, and muscles in addition to cartilage and bone, has multiple embryonic origins and serves many key functions throughout life, including linear growth, mechanical support for movement, a blood and mineral reservoir, and protection of vital organs.

The patterning and architecture of the skeleton occurs during fetal development. During that period, the number, size, and the shape of the future skeletal elements are determined, and this process is under complex genetic control.[4] Uncondensed mesenchyme undergoes cellular condensations (cartilage anlagen) at sites of future bones, and this occurs by two mechanisms.[5] In the process of endochondral ossification, mesenchyme first differentiates into a cartilage model (anlagen), and then the center of the anlagen degrades, mineralizes, and is removed by osteoclast-like cells. This process spreads up and down the bones and allows for vascular invasion and influx of osteoprogenitor cells. The periosteum in the midshaft region of the bone produces osteoblasts, which then synthesis the cortex. This is known as the *primary ossification center*. At the ends of the cartilage anlagen, a similar process leading to the removal of cartilage occurs (secondary center of ossification), leaving a portion of cartilage model "trapped" between the expanding primary and secondary ossification center. This area is referred to as a *cartilage growth plate* or *epiphyses*. There are four chondrocyte cell types in the growth plate: reserve, resting, proliferative, and hypertrophic. These growth plate chondrocytes

undergo a tightly regulated program of proliferation, hypertrophy, degradation, and then replacement by bone, leading to the primary spongiosa. This is the major mechanism underlying skeletogenesis and is the means by which bones increase in length and the articular surfaces increase in diameter. In contrast, the flat bones of the cranial vault and part of the clavicles and pubis form by intramembraneous ossification, in which fibrous tissue, derived from mesenchymal cells, differentiate directly into osteoblasts, which then directly lay down bone. These processes are under specific temporal and genetic control, and abnormalities in the genes that encode these pathways frequently lead to skeletal dysplasias.[5]

Cartilage Structure

Collagen accounts for two-thirds of the adult weight of adult articular cartilage and provide significant strength and structure to the tissue. Collagens are a family of proteins that consist of single molecules (monomers) that associate into three polypeptide chains to form a triple helix structure. In the triple helix, every third amino acid is a glycine residue, and the general chain structure is denoted as Gly-X-Y, where the X and Y amino acids are commonly proline and hydroxyproline. The collagen helix can be composed of identical chains (homotrimeric), as in type II collagen, or can consist of different collagen chains (heterotrimeric), as seen in type I collagen.[6]

Collagens are widely distributed throughout the body, and 33 collagen gene products are expressed in a tissue-specific manner, leading to 19 triple-helical collagens. Collagens are further classified by the structures they form in the extra-cellular matrix. The most abundant collagens are the fibrillar types (I, II, III, V, and XI), and their extensive cross-linking provides mechanical strength that is necessary for high-stress tissue, such as cartilage, bone, and skin.[7] Another collagen species is the fibril-associated collagens with interrupted triple helices (FACIT) and include types IX, XII, XIV, and XVI collagens. These collagens interact with fibrillar collagens as well as other extra-cellular molecules, including aggrecan, cartilage oligomatrix protein (COMP), and other sulfated proteoglycans.[8] Types VIII and X collagen are nonfibrillar, short-chain collagens, and type X collagen is the most abundant extra-cellular matrix molecule expressed by hypertrophic chondrocytes during endochondral ossification.[8] The major collagens of articular cartilage are fibrillar collagen, including types II, IX, XI, and X. In developing cartilage, the core fibrillar network is a cross-linked copolymer of types II, IX, and XI collagen,[9] and form the backbone complex to which other structural proteins bind. Mutations in genes that encode these collagens result in varying skeletal dysplasias (Table 105-1) and

TABLE 105-1 Classification of the Chondrodysplasias

Dysplasia	Mode of Inheritance	Gene
Achondroplasia Group		
Achondroplasia	AD	*FGFR3*
Thanatophoric dysplasia, type I	AD	*FGFR3*
Thanatophoric dysplasia, type II	AD	*FGFR3*
Achondroplasia	AD	*FGFR3*
Hypochondroplasia	AD	*FGFR3*
SADDAN	AD	*FGFR3*
Osteoglophonic dysplasia	AD	*FGFR1*
Severe Spondylodyplastic Dysplasias		
Achondrogenesis IA	AR	*TRIP11*
Opsismodysplasia	AR	*INPPL1*
Metatropic Dysplasia Group		
Fibrochondrogenesis	AR	*COL11A1, COL11A2*
Schneckenbecken dysplasia	AR	*SLC35D1, INNPI1*
Metatropic dysplasia	AD	*TRPV4*
Short Rib Dysplasia (Polydactyly) Group		
Short rib polydactyly syndromes, including asphyxiating thoracic dysplasia	AR	*DYNC2H1, NEK1, WDR60, WDR35, IFT80, WDR34, IFT172, TCTEXD1, DYNC2LI1*
Chondroectodermal dysplasia	AR	*EVC1, EVC2*
Thoracolaryngopelvic dysplasia	AD	Unknown
Omodysplasia Group		
Omodysplasia I	AD	Unknown
Omodysplasia II	AR	GPC6
Filamin-Related Disorders		
Atelosteogenesis I	AD	*FLNB*
Atelosteogenesis III	AD	*FLNB*
Larsen syndrome	AD	*FLNB*
Otopalatodigital syndrome type II	XLR	*FLNA*
Osteodysplasty, Melnick-Needles	XLD	*FLNA*
Diastrophic Dysplasia Group		
Achondrogenesis IB	AR	*DTDST*
Achondrogenesis II	AR	*DTDST*
Diastrophic dysplasia	AR	*DTDST*
Recessive multiple epiphyseal dysplasia	AR	*DTDST*

TABLE 105-1 Classification of the Chondrodysplasias—cont'd

Dysplasia	Mode of Inheritance	Gene
Dys-segmental Dysplasia Group		
Dys-segmental dsyplasia	AR	*HSPG2*
Silverman-Handmaker type		
Dyssegmental dsyplasia	AR	*HSPG2*
Rolland-Desbuquois		
Type II Collagenopathies		
Achondrogenesis II	AD	*COL2A1*
Kniest dysplasia	AD	*COL2A1*
Spondyloepiphyseal dysplasia congenital	AD	*COL2A1*
Spondyloepiphyseal dysplasia, Strudwick type	AD	*COL2A1*
Spondyloperipheral dysplasia	AD	*COL2A1*
Arthro-opthamalopathy, (Stickler syndrome)	AD	*COL2A1*
Type XI Collagenopathies		
Stickler dysplasia	AD	*COL11A1*
Otospondylomegaepiphyseal dysplasia (OSMED)	AR	*COL11A2*
Weissenbacher-Zweymuller syndrome	AD	*COL11A2*
Other Spondyloepi-(meta)-physial dysplasias [SE(M)Ds]		
Spondyloepimetaphyseal dysplasia, Pakistani type	AR	*ATPSK2*
Spondyloepiphyseal dysplasia tarda	XLR	*SEDL*
Progressive pseudorheumatoid dysplasia	AR	*WISP3*
Dyggve-Melchior-Clausen dysplasia	AR	*Dymeclin*
Wolcott-Rallison dysplasia	AR	*EIF2AK3*
Acrocapitofemoral dysplasia	AR	*IHH*
Schimke immunoosseous dysplasia	AR	*SMARCAL1*
Sponastrime	AR	Unknown
Spondyloepimetaphyseal dysplasia, with joint laxity	AR	*B3GALT6*
	AD	*KIF22*
Multiple Epiphyseal Dysplasia and Pseudoachondroplasia		
Multiple epiphyseal dysplasia, types Fairbanks and Ribbing	AD	*COL9A1, COL9A2, COL9A3, MATN3, COMP*
Pseudoachondroplasia	AD	*COMP*
Chondrodysplasia Punctata		
Chondrodysplasia punctata, rhizomelic type	AR	*PEX7, DHAPAT, AGPS*
Chondrodysplasia punctata, Conradi-Hunermann type	XLD	*EBP*
Hydrops-ectopic-calcifications-moth-eaten bones	AR	*LBR*
Chondrodysplasia punctata, brachytelephalangic type	XLR	*ARSE*
Metaphyseal Dysplasias		
Metaphyseal chondrodysplasia, type Jansen	AD	*PTHrP*
Eiken dysplasia	AR	*PTHrP*
Bloomstrand dysplasia	AR	*PTHrP*
Metaphyseal chondrodysplasia, type Schmidt	AD	*COL10A1*
Metaphyseal chondrodysplasia, McKusick type	AR	*RMRP*
Metaphyseal chondrodysplasia, with pancreatic insufficiency, and cyclin neutropenia	AR	*SBDS*
Adenosine deaminase deficiency	AR	*ADA*
Spondylometaphyseal Dysplasias		
Spondylometaphyseal dysplasia, type Koslowski	AD	*TRPV4*
Spondylometaphyseal Dysplasia, type corner fracture	AD	Unknown
Brachyolmia Spondylodysplasias		
Brachyolmia (Hobek type) (Toledo type)	AR	Unknown
Brachyolmia (Maroteaux type)	AR	*TRPV4*
Brachyolmia (AD)	AD	*TRPV4*
Mesomelic Dysplasias		
Dyschondroseosis	XLD	*SHOX*
Mesomelic dysplasia, type Langer	XLR	*SHOX*
Mesomelic dysplasia, type Robinow	AD	
	AR	*ROR2*
Acromelic and Acromesomelic Dysplasias		
Acromicric dysplasia	AD	*FBN1*
Geleophysic dysplasia	AR	*ADAMTSL2*
	AD	*FBN1*
Trichorhinophalangeal dysplasia, type I	AD	*TRPS1*
Trichorhinophalangeal dysplasia, type II	AD	*TRPS2*
Acrodysostosis	AD	*PDE4D, PRKAR1A*
Grebe dysplasia	AR	*CDMP1*
Acromesomelic dysplasia, Hunter-Thompson	AR	*CDMP1*
Acromesomelic dysplasia, type Maroteaux	AR	*NPRB*
Dysplasia with Prominent Membranous		

Continued

TABLE 105-1 Classification of the Chondrodysplasias—cont'd

Dysplasia	Mode of Inheritance	Gene
Bone Involvement		
Cleidocranial dysplasia	AD	*CBFA1*
Bent Bone Dysplasias		
Campomelic dysplasia	AD	*SOX9*
Stuve-Wiedemann dysplasia	AR	*LIFR*
Multiple Dislocations with Dysplasias		
Desbuquois syndrome	AR	*CANT1, XYLT1*
Pseudodiastrophic dysplasia	AR	Unresolved
Spondyloepimetaphyseal dysplasia with joint laxity	AR	*B3GALT6*

AD, Autosomal dominant; AR, autosomal recessive; SADDAN, severe achondroplasia with developmental delay and acanthosis nigricans; SP, sporadic; XLR, X-linked recessive; XLD, X-linked dominant.

highlight the importance of these molecules in skeletal development.

Classification and Nomenclature

As mentioned above, in the 1970s there was recognition of the genetic and clinical heterogeneity of these disorders and a new awareness of the complexity of these disorders. As a result, there have been multiple attempts to classify these disorders in a manner that clinicians and scientists could effectively use to diagnose and determine their pathogenicity (International Nomenclature of Constitutional Diseases of Bone, 1970, 1977, 1983, 1992, 2001, 2005, and 2010).[2] The initial categories were purely descriptive and clinically based. With the recent explosion in determining the genetic basis of these diseases, the classification has evolved into one that combines the older clinical one (including the eponyms and Greek terms) and also blends these disorders into families that share a molecular basis or pathway. Some of the chondrodysplasia families are listed in Table 105-1. The most widely used method for differentiating the skeletal disorders has been through the detection of skeletal radiographic abnormalities. Radiographic classifications are based on the different parts of the long bones that are abnormal (epiphyses, metaphyses, diaphyses) (Figure 105-1). These epiphyseal, metaphyseal, and diaphyseal disorders can be further differentiated depending on whether or not the spine is involved (spondyloepiphyseal, spondylometaphyseal dysplasias, or spondyloepimetaphyseal dysplasias). Moreover, each of these classes of these disorders can be further differentiated into distinct disorders based on other clinical and radiographic findings.

Clinical Evaluation and Features

The skeletal dysplasias are generalized disorders of the skeleton and usually result in disproportionate short stature. Affected individuals usually present with the complaint of disproportionate short stature, and this finding needs to be documented on the appropriate growth curves for sex and ethnicity if possible. As a general comment, most individuals with disproportionate short stature have skeletal dysplasias, and those with proportionate short stature have endocrine, nutritional, prenatal-onset growth deficiency, or other nonskeletal dysplasia genetic disorders. However, there are exceptions to the rule, such as congenital hypothyroidism, which is associated with disproportionate short stature, and disorders such as mild osteogenesis imperfecta and hypophosphatasia can be associated with relatively normal body proportions.

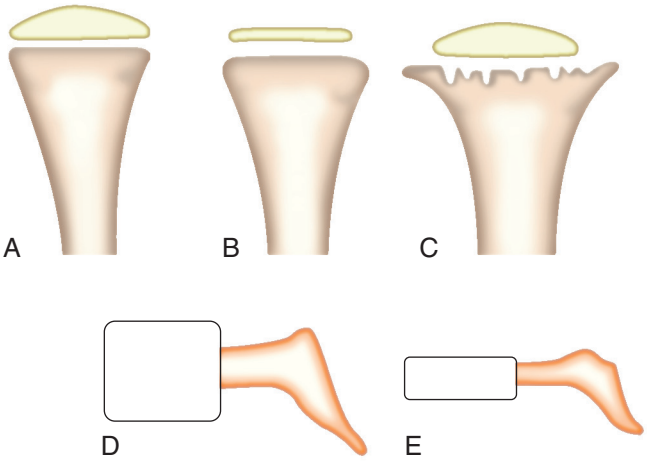

Figure 105-1 Classification of chondrodysplasias based on radiographic involvement of the long bones **(A-C)** and vertebrae (**D** and **E**). **A** and **D** are normal. **B,** epiphyseal abnormality. **C,** metaphyseal abnormality. **E,** spondylo-abnormality.

A disproportionate body habitus may not be immediately visible on physical examination. Therefore the physician must take anthropodemetric measurements, such as upper/lower segment (U/L) ratio, sitting height, and arm span, when considering the possibility of a skeletal dysplasia, and measurements should be taken in centimeters. Sitting height is an accurate measure of head and trunk length, but it requires special equipment for precise measurements. Upper/lower ratios are easy to obtain and provide an accurate measurement of proportion. The lower segment is measured from the symphysis pubis to the floor at the inside of heel. The upper segment is measured by subtracting the lower segment measurement from the total height. For example, a Caucasian child between the ages of 8 to 10 years has a U/L segment ratio of approximately 1.0 and an U/L segment ratio of 0.95 as an adult. Individuals seen with disproportionate short stature will have altered ratios depending on whether they have short limbs, short trunk, or both. For example, an individual with short limbs and relatively normal trunk will have an increased U/L segment ratio, and an individual with relatively normal limbs but a short trunk will have a diminished U/L segment ratio (Figure 105-2). Another means of determining whether

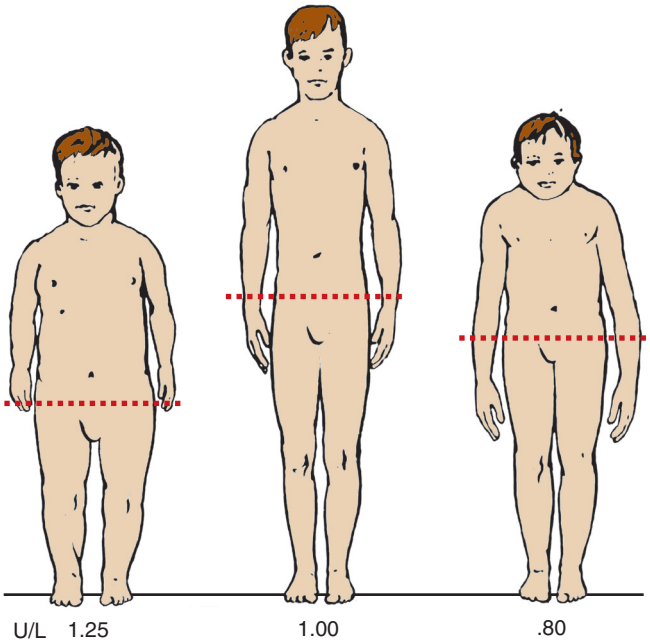

Figure 105-2 Upper segment length/lower segment length in 8- to 10-year-old individuals with short-limb and short-trunk dwarfism. The child on the left has short limbs and an increased upper/lower ratio; the child on the right has a short trunk and reduced upper/lower ratio.

there is disproportion is based on arm span measurements, which are measured from tip to tip of the third finger. Arm span length is typically very close to total height (1:1) in an average-proportioned individual. A short-limbed individual will have an arm span considerably shorter than their height.

As in any disorder that has a genetic basis, it is critical for the physician to obtain an accurate family history, and this should include any history of previously affected children or parental consanguinity. The skeletal dysplasias are genetically heterogenous and can be inherited as autosomal dominant, autosomal recessive, X-linked recessive, and X-dominant disorders, and rarer genetic mechanisms of disease, including germline mosaicism, somatic mosaicism, uniparental disomy, and microdeletion syndromes, have been seen. For many patients and families, accurate diagnosis and recurrence risk can have significant impact on their reproductive decisions. Another consideration for patients with short stature is that there is increased nonassertive mating, which leads to reproductive outcomes that have been previously unknown.[10] For example, homozygous achondroplasia is lethal, and many newborns who inherit two dominant mutations (compound heterozygotes) do quite poorly because of increased lethality and severe effects on the skeleton.[11] The physician should also obtain accurate history relative to the onset of short stature and whether it developed immediately in the postnatal period or was noticed at age 2 or 3 years. Of the 450 skeletal dysplasias, approximately 100 of them have onset in the prenatal period, but many do not manifest disproportionate short stature and joint discomfort until childhood.[2]

A detailed physical examination may reveal a diagnosis or help differentiate the most likely group of possible diagnoses. It is critical that once disproportion and short stature has been established and the limbs are involved, to determine which segment is involved: upper segment (rhizomelic; humeri and femora), middle segment (mesomelic; radii, ulnae, tibiae, and fibulae), and distal segment (acromelic; hands and feet). Numerous head and facial dysmorphisms are seen in the skeletal disorders. Affected individuals frequently have disproportionately large heads or relative macrocephaly. Frontal bossing of the metopic bossing and flattened nasal bridge is very characteristic of achondroplasia, one of the most common skeletal dysplasias.[12] Cleft palate and micrognathia are commonly found in the type II collagen abnormalities, abnormally flattened of the midface with a turned-up nose is frequently found in the chondrodysplasia punctata disorders,[13] and abnormal swollen pinnae are seen in diastrophic dysplasia.[14] Individuals with skeletal dysplasias should be screened for ophthalmologic and hearing abnormalities because some of these disorders are associated with eye abnormalities and hearing loss.

Further evaluation of the hands and feet can lead to further differentiation of these disorders. Postaxial polydactyly is characteristically found in chondroectodermal dysplasia and the short-rib polydactyly syndrome disorders (see Table 105-1). Short, hypermobile, radially displaced thumbs and medially deviated halluxes are seen in diastrophic dysplasia. Nails can be abnormally hypoplastic in chondroectodermal dysplasia and short and broad in cartilage hair hypoplasia. Club feet or equinovarus may be seen in many disorders, including Kniest dysplasia, spondyloepiphyseal dysplasia congenita, Larsen syndrome, more severe forms of osteogenesis imperfecta, and diastrophic dysplasia. Bone fractures occur most commonly in two types of disorders: those that result from undermineralized bone (osteogenesis imperfecta, hypophosphatasia, achondrogenesis IA), or those that result from overmineralized bone (osteopetrosis syndromes and dysosteosclerosis).

Other organ systems, beyond the skeleton, can be involved though not commonly. Congenital cardiac defects are seen in chondroectodermal dysplasia (atrial septal defect), the short-rib polydactyly syndrome disorders (complex outlet defects, including isolated ventricular septal defects) and in Larsen syndrome (ventricular septal defect). Gastrointestinal anomalies are rare among the skeletal disorders, but congenital megacolon can be seen in cartilage hair hypoplasia, malabsorption syndrome in Shwachman-Diamond syndrome, and omphaloceles in otopalatodigital syndrome and atelosteogenesis I.

Diagnostic Tests and Diagnosis

After obtaining a thorough family history and physical examination, the next step is to obtain a full set of skeletal radiographs or genetic skeletal survey. A full series of skeletal views, including anterior, lateral, and Towne views of the skull, anterior and lateral views of the entire spine, and anteroposterior pelvis and extremities, with separate views of the hands and feet, is optimal, especially after the newborn period. Most of the important clues to diagnosis are in skeletal radiographs that are obtained before puberty. Once the epiphyses have fused to the metaphyses, determining the precise diagnosis can be exceedingly challenging. If an adult is evaluated, all attempts should be made to obtain any available childhood radiographs. There are many subtle

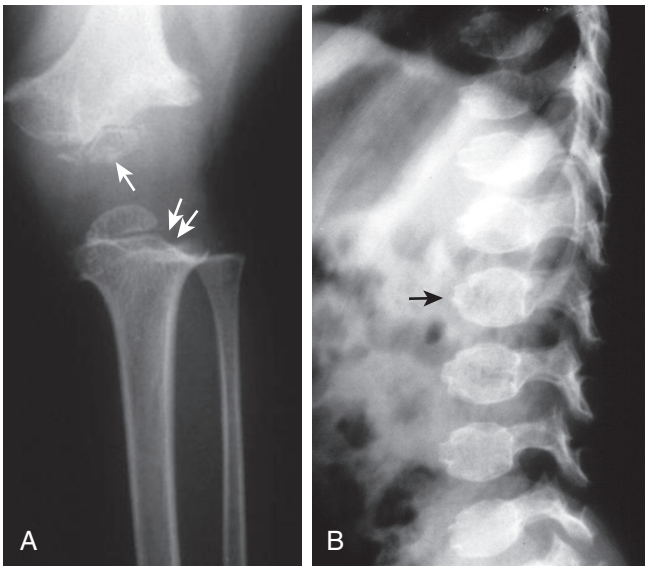

Figure 105-3 Radiographs showing abnormalities. **A,** Distal femur and proximal tibia and fibula showing small irregular epiphyses *(single arrow)* and irregular metaphyses *(double arrows)*. **B,** Lateral view of the spine showing abnormally rounded vertebral bodies with anterior central beaking *(arrow)*.

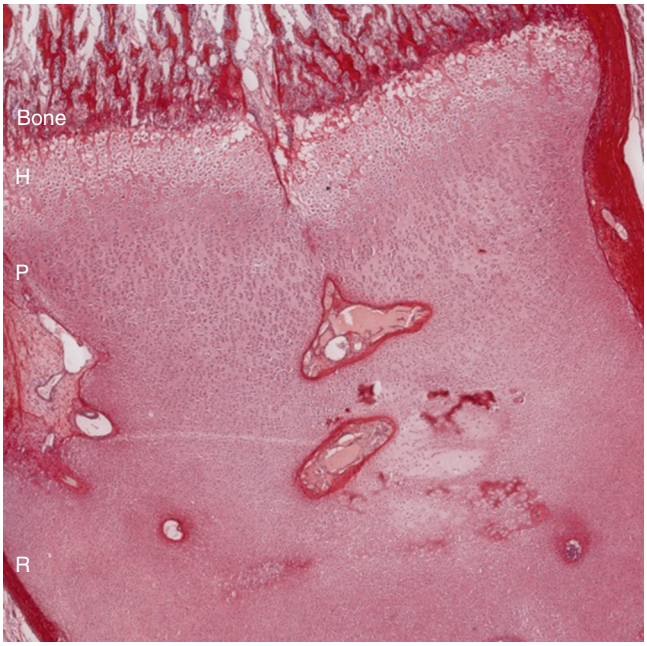

Figure 105-4 Histologic analysis of a control 17-week human fetal growth plate stained with picrosirius red, showing the morphology of the growth plate. The defined zones of the growth plate are labeled, *H*, hypertrophic, *P*, proliferative, and *R*, resting.

clues in these skeletal radiographs that can lead to a precise diagnosis. For example, punctuate calcifications in the areas of the epiphyses in the chondrodysplasia punctata disorders, which are not seen in adulthood; multiple ossification centers of the calcaneus in more than 20 disorders[15]; and the pattern of hand shortening can aid in differentiating many disorders.

After obtaining radiographs, the physician should pay close attention to the specific parts of the skeleton (spine, limbs, pelvis, skull) involved and to the location of the lesions (epiphyses, metaphyses, and spondylcomponents) (Figure 105-3). As mentioned in preceding text, these radiographic abnormalities can change with age. If possible to obtain, radiographs of patients across a few ages will aid in diagnosis. Fractures can be seen in osteogenesis imperfecta (all types; see Table 105-1) and severe hypophosphatasia. In older individuals, fractures may be seen in disorders associated with increased mineralization, such as the osteopetrosis syndromes.

Morphologic studies of chondroosseus tissue have revealed specific abnormalities in many of the skeletal dysplasias.[16] In these disorders, histologic evaluation of chondroosseous morphology can aid in making an accurate diagnosis, and absence of histopathologic alterations can rule out diagnoses (Figure 105-4). These studies need to be performed on cartilage growth plate, and although commonly performed on perinatal lethal skeletal disorders at time of autopsy, obtaining growth plate histology on individuals with nonlethal disorders is difficult. If affected individuals (children) are undergoing surgery, an iliac crest biopsy can be evaluated, although admittedly this is performed with markedly less frequency than in the past, particularly while our molecular understanding has markedly increased. However, histomorphology studies done on these disorders have led to important insights on the pathogenesis of these disorders. On morphologic grounds, the chondrodysplasias can be broadly classified into those disorders that (1) have a qualitative abnormality in endochondral ossification, (2) have abnormalities in cellular morphology, (3) have abnormalities in matrix morphology, and (4) in which the abnormality is primarily localized to the area of chondroosseous transformation. For example, in thanatophoric dysplasia, there is a defect in endochondral ossification with a very short, if almost hypertrophic, zone, a shortened proliferative zone, and overgrowth of the periosteum. In pseudoachondroplasia, there is a distinct lamellar pattern (alternating electron-dense and electron-lucent lamellae) in the rough endoplasmic reticulum of chondrocytes and a grossly abnormal matrix in diastrophic dysplasia, which leads to a characteristic ring around the chondrocytes. All of these findings are characteristic and diagnostic for these disorders and illustrates how morphology studies can play in integral part in the investigation of these disorders. Further, disorders across a phenotypic spectrum have been placed in bone families based on similar cartilage growth plate morphologic abnormalities.

There has been significant progress in gene identification in these disorders, which has impact for affected individuals. As illustrated in Table 105-1, for those disorders in which the gene is identified, molecular diagnostic testing is potentially available. Molecular diagnosis can be used to confirm a clinical and radiographic diagnosis, predict carrier status in those families at risk for a recessive disorder, and, for some individuals, allow prenatal diagnosis of at-risk fetuses. With commercial availability of whole-exome sequence analysis, many high and low bone mass parallel sequencing panels are available, as well as whole-exome sequence analysis for rare disorders not available on panels. If there is no question regarding definitive diagnosis, then disease genes can be directly interrogated. GeneTests (www.genetests.org) is a

publically funded medical genetics website developed for physicians that provides information on specific diseases and available genetic testing.

Treatment

The optimal management of this diverse set of disorders requires an understanding of their medical, skeletal, and psychosocial consequences. This is often best accomplished by centers that have a multidisciplinary approach, which include adult and pediatric physicians, as well as a group of physicians, geneticists, orthopedists, rheumatologists, otolaryngologists, neurologists, neurosurgeons, and ophthalmologists who are committed to the care of these patients.

Most medical complications in these disorders result from orthopedic complications, and they vary depending on the specific disorder. For example, in disorders associated with significant odontoid hypoplasia, such as Morquio disease, type II collagenopathies, metatropic dysplasia, and Larsen syndrome, flexion-extension films should be monitored at regular intervals to assess C1-C2 subluxation. If there is evidence for subluxation, surgery for C1-C2 fixation is indicated. Many geneticists support flexion and extension radiographic evaluation, including MRI of the neck in all cases of skeletal dysplasias, because so many of these disorders have cervical vertebral abnormalities.[17] Genu varum, lateral curvature of the lower extremity, is common in many skeletal disorders because of overgrowth of the fibula. This causes knee or ankle pain in many individuals, especially children, and consideration should be made for correction by osteotomies. Children and adults with skeletal dysplasias should have regular eye and hearing examinations because they are at increased risk for myopia, retinal degeneration, glaucoma, and hearing loss, depending on the disorder.

Frequently, patients with these disorders have significant joint pain and, in some cases, joint limitations. Because most of these disorders result from mutations in genes critical to cartilage function, the cartilage at the joint surfaces may not provide adequate support and cushioning function. Many of these patients seek attention for joint pain. Evaluation should include radiographic views and MRI, when appropriate, to determine the etiology of the pain. In some disorders (e.g., the type II collagenopathies, pseudoachondroplasia, multiple epiphyseal dysplasia, and cartilage hair hypoplasia), by adulthood so little cartilage remains at the knee or hips that joint replacement is indicated for pain relief. Last, weight control in adults with short stature is an ongoing issue and contributes to inactivity, loss of function, adult-onset diabetes, hypertension, and coronary disease.[18]

Achondroplasia is the most common of the nonlethal skeletal dysplasias (approximately 1/20,000) and serves as an example on how to approach these disorders, particularly because the incidence and type of medical complications change during the life span of the individual. The majority of these individuals are of normal intelligence, have a normal life span, and lead independent and productive lives. The mean final height in achondroplasia is 130 cm for men and 125 cm for women, and specific growth charts have been developed to document and track linear growth, head circumference, and weight in these individuals.[19,20]

In early infancy, there is potentially serious compression of the cervicomedullary spinal cord secondary to a narrow foramen magnum, cervical canal, or both. Clinically, these infants show central apnea, sleep apnea, profound hypotonia, motor delay, or excessive sweating. MRI with flow studies is necessary to document the obstruction and, if present, requires decompression surgery. Other complications include upper airway obstruction, thoracolumbar kyphosis, and hydrocephalous in a small number of individuals.[21] From early childhood and while the child begins to walk, several orthopedic manifestations occur, including progressive bowing of the legs because of fibular overgrowth, lumbar lordosis, and hip flexion contractures. Recurrent ear infections lead to chronic serous otitis media and deafness. Tympanic membrane tube placement is indicated in many of these patients. Craniofacial abnormalities lead to dental malocclusion, and appropriate treatment is necessary. As adults, the main potential medical complication is impingement of the spinal root canals, and this can be manifested by lower limb paresthesias, claudication, clonus, bladder, or bowel dysfunction. It is critical that these complaints are addressed because without appropriate decompression surgery, paralysis of the spinal cord can result.[21]

Growth hormone has not been effective in increasing height in this disorder.[22] Surgical limb lengthening has been used successfully to increase limb length by as much as 12 inches,[23] but patients need to recognize that this technique needs to be done during the teen years, is performed during a 2-year period, and is associated with complications. Because of the discovery of the disease gene in 1994,[24] the molecular consequences of the activating mutation in fibroblast growth factor receptor 3 gene *(FGFR3)* have been elucidated. Although the mutation has numerous effects on receptor kinase signaling pathways, increased activation of ERK (mitogen-activated protein kinase) is responsible for much of the proliferation defect seen in achondroplasia cartilage growth plates.[25] Inhibitors of the pathway have been identified and potential treatments are being proposed.[26]

Throughout their lives, individuals with achondroplasia, other skeletal dysplasias, and their families experience various psychosocial challenges.[27] This can be addressed by specialized medical and social support systems. Interactions with advocacy groups such as *Little People of America* (*LPA*; http://www.lpaonline.org) can provide both emotional support and medical information.

Biochemical and Molecular Abnormalities

Based on clinical, radiographic, and histomorphologic similarities, skeletal dysplasias have been placed into bone dysplasia families.[28] These families share a common pathophysiologic or pathway mechanisms. In recent years, there has been an explosion in our understanding of the basic biology of these disorders. This has resulted from advances in the human genome project that improved various methodology, including candidate gene approach, linkage analysis, positional cloning, human/mouse synteny, whole-exome and whole-genome analysis, allowing identification of the responsible disease genes (see Table 105-1). With gene discovery in more than 350 of these osteochondrodysplasias, these genes can be placed into several categories

designed to understand their pathogenesis: (1) defects in extra-cellular proteins, (2) defects in metabolic pathways (enzymes, ion channels, and transporters), (3) defects in folding and degradation of macromolecules, (4) defects in hormones and signal transduction, (5) defects in nuclear proteins, (6) defects in oncogenes and tumor suppressor genes, (7) defects in RNA and DNA processing molecules, (8) defects in intra-cellular structural proteins, (9) defects in chaperones, (10) defects in ciliary components, and (11) genes of unknown function. There are still skeletal dysplasias for which the disease-producing genes are unknown. Below are just some examples of the molecular mechanisms involved in the skeletal dysplasias.

DEFECTS IN EXTRA-CELLULAR STRUCTURAL PROTEINS

Type II Collagen and Type XI Collagen

Because type II collagen was found primarily in cartilage, the nucleus pulposus, and the vitreous of the eye, it was hypothesized that skeletal disorders with significant spine and eye abnormalities would result from defects in type II collagen. Indeed, type II collagen defects have been identified in a spectrum of disorders ranging from lethal to mild arthropathy, which include achondrogenesis II, hypochondrochogenesis, spondyloepiphyseal dysplasia congenital, spondyloperipheral, spondyloepimetaphyseal dysplasia, Strudwick type, Kniest dysplasia, Stickler syndrome, and "precocious" familial arthropathy. These disorders are referred to as *type II collagenopathies*, and they all result from heterozygosity for mutations in the gene *COL2A1*, which encodes type II collagen.[29,30] Biochemical analysis of cartilage derived from these individuals shows electrophoretically detectable abnormal type II collagen. Further, type I collagen is not normally present in cartilage; however, in the presence of abnormal type II collagen, there is increased type I collagen in the growth plate.

Mutations that result in a substitution for a triple-helical glycine residue appear to be the most common type of mutation.[31-33] There are some correlations between the location of the mutation and the disease phenotype. In spondyloepiphyseal dysplasia congenita (SEDC), the glycine substitutions are scattered throughout the molecule; however, in Kniest dysplasia, the mutations are in the more amino-terminal end of the molecule.[34-36] Stickler syndrome is genetically heterogenous and results from mutations in *COL2A1* and *COL11A1*, and non-ocular forms in *COL11A2*.[37,38] In Stickler syndrome, the *COL2A1* and *COL11A1* mutations tend to be nonsense mutations resulting in premature translation stop codons; however, patients with *COL11A1* mutations tend to have a more severe eye phenotype and hearing loss than patients with *COL2A1* mutations.

Individuals heterozygous for various *COL11A2* mutations have a non-ocular form of Stickler syndrome, which is consistent with the absent expression of *COL11A2* in the vitreous humor. Otospondylomegaepiphyseal dysplasia (OSMED) is a rare autosomal recessive disorder caused by loss of function mutations in *COL11A2*.[39] This disorder has radiographic similarities to Kniest dysplasia but is associated with profound sensorineural hearing loss and lack of ocular involvement. To add to the spectrum of type XI mutations, both dominantly and recessively inherited mutations in *COL11A1* and *COL11A2*, respectively, can produce the very severe skeletal dysplasia, fibrochondrogenesis.[40,41]

Cartilage Oligomeric Matrix Protein

Heterozygosity for mutations in COMP lead to both pseudoachondroplasia and multiple epiphyseal dysplasia.[42] COMP is a member of the thrombospondin family of protein and consists of an epidermal growth factor domain and a calcium-binding calmodulin domain.[43] In both pseudoachondroplasia and MED, disease-producing mutations occur in the calmodulin domain, with a minority in the globular carboxyterminal domain. Both these disorders are associated with early-onset osteoarthritis, particularly of the hips and the knee, leading to joint replacements in many individuals in early adulthood.[44]

Conclusion

Although these osteochondrodysplasias are relatively rare disorders, affected individuals have significant skeletal complications throughout their lives, first because of patterning defects, then effects on linear growth, and, finally, loss of normal structural cartilage as a cushion later in life. The explosion in delineating molecular defects has shown the complexity of cartilage as a tissue and the large number of cellular processes necessary for a normal skeleton.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI) is a heritable disorder of bone and was one of the first genetic disorders hypothesized to be a defect in collagen.[45] Although an osteochondrodysplasia, it will be discussed separately from the chondrodysplasias delineated above. OI is actually a generalized disorder of connective tissue that predominantly affects the skeletal system and affects a significant numbers of individuals (estimates at approximately 1/20,000 individuals)

Initially, there were four types of recognized OI in the clinical classification of Sillence.[46] However, there are now numerous types of recognized OI on the basis of expanding genetic heterogeneity, yet most of the forms of OI can still be classified into mild, moderate, severe, and lethal. Because there is enormous clinical variability in these types, the subtypes will be discussed separately (Table 105-2). However, these disorders all share the same phenotypic finding of hypomineralization of the skeleton, although interesting bone quality is associated with overbrittleness.[47]

Mild Osteogenesis Imperfecta (Type I OI)

Affected individuals with type I OI disease have relatively mild severity in terms of their clinical course, the extent of skeletal deformity, and the radiologic appearance of the skeleton (see Table 105-2). They also account for the vast majority of individuals with OI. Individuals usually have mild short stature for their age or their unaffected family members, but are not as severe as seen in the other forms. Many of these individuals experience numerous fractures, especially in childhood, and it is common for

TABLE 105-2 Classification and Molecular Basis of Osteogenesis Imperfecta (OI)

Sillence Classification	OI Phenotypic Grouping	Mode of Inheritance	Biochemical Findings	Gene(s)	Mechanisms
I	Mild	AD	50% reduction in type I collagen synthesis	*COL1A1* *COL1A2*	Structural defects Haploinsufficiency
IV	Moderate	AD AR	Structural alterations of type I collagen chains; overmodification	*COL1A1* *COL1A2* *TMEM38B* *SP7*	Structural defects
III	Severe progressive deforming	AD AR	Structural alterations of type I collagen chains; overmodification Structural alterations of type I collagen chains; overmodification Delayed processing of type I procollagen Normal type I collagen biochemical analysis Distinct bone histology	*COL1A1* *COL1A2* *CRTAP* *P3H1* *PPIB* *BMP1* *FKBP10* *SERPINH1* *WNT1* *SERPINF1* *PEDF*	Structural defects 3-Hydroxylation defects Molecular chaperones Osteoblast maturation
II	Perinatal lethal	AD AR	Structural alterations of type I collagen chains; overmodification	*COL1A1* *COL1A2* *CRTAP* *P3H1* *PPIB*	Structural defects 3-Hydroxylation defects
V	Hypercallus formation Joint contractures (Bruck syndrome) Prenatal cortical hyperostosis (Caffey disease)	AD AR AD		*IFITM5* *PLOD2* *FKBP10* *COL1A1*	

*Sillence classification: original osteogenesis imperfecta classification.
AD, Autosomal dominant; AR, autosomal recessive.

them to have has as many as twenty fractures by the age of five.

The disorder is autosomal dominant, and in many cases, the individual is the first affected in their family. Their sclerae are blue that becomes gray to pale blue in adulthood. Arcus senilis not related to lipid abnormalities may occur in some patients. Other reported ocular defects include scleromalacia, keratoconus, and retinal hemorrhage.[48] Their teeth frequently show dentinogenesis imperfecta (DI) because of the effects of mutation on the tooth dentin.[49] The deciduous and permanent teeth have an opalescent and translucent appearance, which tends to darken with age. The enamel is normal, but the dentin is dysplastic; chipping of enamel occurs, and the teeth are subjected to erosion and breakage. Affected individuals' teeth appear discolored or gray; this finding is variable in the disorder but does cosegregate in families with OI. DI can be seen in all forms of OI.

During the second and third decades of life, a characteristic high-frequency sensorineural or mixed hearing loss can be detected.[50] The incidence of mitral valve prolapse is not increased in these patients compared with the population at large, but individual kindreds with increased diameter of the aortic root or patients with aortic regurgitation have been reported.[51] Many patients complain of easy bruising, and this may result from the effects of mutation on both skin and the vessels below.

Mildly affected patients may not have fractures at birth, although there is occasionally a fracture of a clavicle or extremity during delivery. Radiographically, affected newborns have wormian bones seen on lateral views of the skull, with significant osteopenia seen through the skeleton, especially the spine. The frequency of fracture thereafter depends on the child's activity, the need for immobilization after lower extremity fractures, and the attitude of the family toward independent activity. In general, these patients may experience 5 to 15 major fractures before puberty, as well as several minor traumatic fractures of the digits or the small bones of the feet. Characteristically, the fracture rate falls dramatically after puberty, only to increase during later life. Mild scoliosis approximating 20 degrees is common. Osteopenia is observed in vertebral bodies and the peripheral skeleton and progresses with age. It is remarkable that in type I OI the long bones usually heal with no significant deformity. When compared with more severe phenotypes, children with type I OI only infrequently require the insertion of intramedullary rods and almost never experience nonunion at a fracture site.

Although osteopenia with rarefaction of the medullary space and cortical thinning are observed in radiographs, many type I cases are so mild as to be missed on routine radiographic examination. Measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) at any age discloses a significant decrease in bone mass. T scores (i.e., standard deviation from the young-adult mean BMD) are frequently in the range of −2.5 to −4.0 at the lumbar spine or proximal femur, consistent with the diagnosis of osteoporosis as defined by the World Health Organization (WHO). Low BMD in children with recurrent fractures may assist in identifying those with OI.

Molecular Pathology

Type I OI results from mutations affecting the COL1A1(I) and COL1A2(I) polypeptide chains of type I collagen. Cultured fibroblasts from individuals with mild OI synthesize low amounts (approximately one-half) of the expected amounts of type I collagen. Most of the reported mutations in type I OI are nonsense and frameshift mutations and thus are predicted to lead to premature termination codons, although there are some exceptions.[52,53]

Lethal Osteogenesis Imperfecta (Type II OI)

Approximately 10% of patients with OI have the severe neonatal form of the disease, lethal osteogenesis imperfecta. Most cases result from sporadic mutations, however, recessively inherited forms of the disease has recently been documented.[54-56] These infants are seen with severe bone fragility, multiple intrauterine fractures at various stages of healing, deformed extremities and, occasionally, hydrops fetalis. Radiographic features include wormian bones, multiple fractures, crumbled bones and characteristic beading of the ribs caused by healing callus formation.

Molecular Pathology

Most cases occur de novo as new dominant mutations; however, autosomal recessive forms have been established, as has recurrence based on germline mosaicism.[57] The biochemical abnormality in lethal OI is the inability to synthesize and secrete normal type I collagen.[57] As a result, the amount of type I collagen in bone is low, much of the secreted collagen is abnormally overmodified, and the quantity of the minor collagens, types III and V, is relatively high. Bone collagen fibers are thinner than normal, and at the intra-cellular level type I collagen in retained within dilated endoplasmic reticulum.

Similar to most cases of OI, mutations in the genes encoding COL1A1 and COL1A2A lead to the dominant or de novo form of lethal OI.[58] Single glycine substitution with the Gly-X-Y triplet of either *COL1A1*and *COL1A2* lead to this form of OI, as do some small deletions, all producing severe effects on the triple helix. Recessive form accounts for a small number of these cases and the involved genes are listed in Table 105-2. Some of these recessive forms result from mutations in the genes encoding either *CRTAP* (cartilage-associated protein), *P3H1* (prolyl-3-hydroxylase 1), or *PPBI* (Cyclophilin B). These molecules form a complex that hydroxylate (add an –OH group) to a third-position residue at proline 986 (Pro986). This modification of a single residue is thought to stabilize the collagen helix, although the mechanism of disease production is probably much more complicated, and this complex may act as a chaperone complex.

Severely Deforming Osteogenesis Imperfecta (Type III OI)

The deforming variant of osteogenesis imperfecta is the classic form of OI. Similar to lethal OI (type II OI), most cases are inherited as autosomal dominant (or de novo), although recurrent cases based on autosomal recessive inheritance resulting from mutations in numerous recessively inherited genes have been recently demonstrated (see Table 105-2). This variant of OI is characterized by severe deformity of the limbs and marked kyphoscoliosis, thorax deformity, and significant short stature. The extent of growth retardation is remarkable, and in many adults the height may not surpass 3 ft (90 to 100 cm). Abnormal cranial molding occurs in utero and during infancy, producing frontal bossing and a characteristic triangular-shaped facies. Radiographically, wormian bones and delayed closure of the fontanelles may be observed well into the first decade.

Pulmonary function can be diminished because of distortion of the spine and thorax and can progress with time and lead to restrictive lung disease and sleep apnea. Unfortunately, because of diminished vital capacity, pulmonary insufficiency is a leading cause of death in subjects with type III OI. Respiratory compromise develops in many patients with scoliosis greater than 60 degrees, creating a need for pulmonary investigations. Many of these individuals need supplemental oxygen.

Platybasia resulting from soft bone at the base of the skull may cause the external ear canals to slant upward while the base of the skull sinks on the cervical vertebrae. This distortion may lead to communicating or obstructive hydrocephalus, cranial nerve palsies, and upper and lower motor neuron lesions. Headache, diplopia, nystagmus, cranial nerve neuralgia, decline in motor function, urinary dysfunction, and respiratory compromise are complications of basilar invagination.[59] As opposed to type I OI, most affected patients with type III OI have white sclera as adults. Approximately 25% of patients with type III OI have dentinogenesis imperfecta, necessitating constant dental care throughout childhood. Severe hearing impairment occurs in 10% of patients, although milder degrees of hearing loss are more common.

The skeleton in these patients has significant osteopenia, leading to multiple fractures in the upper and lower extremities and vertebral bodies, particularly before puberty. Unlike type I OI, in which fractures tend to heal without deformity, fractures in type III OI frequently lead to skeletal deformity. Radiographs of the skeleton reveal marked osteopenia, thinning of cortical bone, narrowing of the diaphysis, widening of the metaphysis, which merges into a dysplastic epiphyseal zone filled with whorls of partially calcified cartilage (i.e., popcorn deformity).[60] Osteoporosis leads to collapse of vertebral end plates contributing to worsening kyphoscoliosis. Pectus excavatum or pectus carinatum adds to thoracic deformity.[61] In addition, lack of weight bearing increases the severity of osteoporosis and increases the risk of fracture. Many of the individuals become wheelchair bound at an early age or walk with mechanical assistance.

Molecular Pathology

The molecular basis of type III OI is very similar to type II OI. Most of the cases result from heterozygosity for mutations in *COL1A1* and *COL1A2*. These mutations are glycine substitutions scattered through the triple helix, as well as in-frame deletions. As in type II OI, familial

recurrences result from recessively inherited mutations in numerous genes listed in Table 105-2.

Osteogenesis Imperfecta of Moderate Severity (Type IV OI)

Clinically, the phenotype of patients with moderately severe OI (type IV OI) falls between the milder type I and type III OI, and this diagnosis is somewhat subjective. In most cases, this type is usually inherited in an autosomal dominant fashion. Fractures are rarely at birth, and some patients may not have the initial fracture until later in the first decade. The extent of skeletal deformity involving the spine, thorax, and extremities is usually intermediate between that of types I and III OI, and these patients have short stature and frequently have scoliosis. The patients may have some mild facial dysmorphisms but not as severe as type III OI. Hearing loss occurs but less than in types I and III OI.

Most fractures occur during childhood and may reoccur during the post-menopausal period in women or in men older than age 50 years.[61] Long-bone deformity tends to develop after fractures, which may lead to a difficulty in ambulation. Radiographs of the long bones and vertebral bodies demonstrate marked osteopenia with vertebral collapse. Although there is marked cortical thinning, bowing, and coarsening of trabeculae, the overall architecture of the bone is normal.

Molecular Pathology

The molecular mechanisms for type IV OI are similar to the other forms. The mutations are in *COL1A1* and *COL1A2* and include glycine substitution and in-frame deletions. At the present time, there is no evidence for an autosomal recessive form of type IV OI.

Type V Osteogenesis Imperfecta

This phenotype was reported by in 2000 as a variant within the heterogeneous group classified under type IV OI.[62] In the initial report of seven patients with OI, the phenotype was distinguished by the following criteria: moderate fracture history, hyperplastic callus formation, limitation in forearm pronation and supination due to intramembraneous bone formation at the joint, normal sclera, and no DI. Bone biopsy showed a meshlike appearance of irregularly spaced lamellae, different from the woven bone seen in types II, III, and IV OI. This etiology of this rare form has been established and results from heterozygosity for mutations in *IFITM5*.[63]

Histopathology of Bone in Osteogenesis Imperfecta

The range of histologic appearances of bone in the different OI phenotypes is as variable as the clinical phenotypes. Undermineralization and overmineralization of bone have been recognized within the same specimen.[47] Bone histomorphology appears relatively normal in type I OI, but osteopenia caused by thin lamellar plates and diminished cortical width is evident. Immature woven bone and lamellar disarray are characteristic of more severe OI phenotypes.[47]

Treatment

During the years, there have been multiple attempts to treat OI with a variety of vitamins, hormones, and drugs, none of which has been successful. The list includes administration of mineral supplements, fluoride, androgenic steroids, ascorbic acid, and vitamin D. During the last 15 years, bisphosphonates administered parenterally to children has demonstrated favorable results. Intravenously administered bisphosphonate pamidronate increased bone mass, decreased skeletal pain, and decreased fracture incidence in children with severe OI.[64] Dosage regimens in different series for children and adults have varied from 1 mg/kg to 3 mg/kg, administered intravenously at 2- to 4-month intervals, and lower-dosage regimens also have been reported.[64] In general, reports indicate a significant increase in bone mass in children and a decrease in fracture rate. The effect is most marked in the spine, where vertebral remodeling may improve vertebral height. Metabolic studies by have demonstrated a decrease in serum ionized calcium and increase in serum parathyroid hormone (PTH). The major side effects of intravenous (IV) bisphosphonate treatment involve the acute phase response (24 hours after infusion) and the occurrence of otitis and vestibular imbalance in a small number of patients. The currently recommended treatment regimen includes the use of a bisphosphonate with adequate calcium and vitamin D supplementation to avoid the occurrence of hypercalciuria and to maintain serum vitamin D levels within normal limits. Recently, the use of anabolic treatment to build bone has been tested by using teriparatide in adult patients in OI, and the study showed that patients with mild OI, but not severe OI, benefited from treatment.[65]

The use of surgery to correct deformities and to facilitate weight bearing has been the subject of several reviews.[66] Multiple osteotomies and realignment of a deformed bone over intramedullary rods is an option for many children with severe bowing.[67] Indications include frequent fractures at the apex of the bow, impaired standing, or limb-length inequality resulting from bowing.[68] Expanding (telescoping) rods are best for growing children, for they require fewer revisions. Spinal deformities are common and usually progressive. Surgical stabilization is most advisable in the teen years or early adulthood when patients are best able to tolerate these complex reconstructions.[69] Early basilar invagination may be halted with prophylactic posterior fusion of the occipital-cervical junction with plate fixation.[70] Patients with severe brain stem compression may require anterior transoral decompression, as well as posterior instrumented fusion. Patients with various types of OI appear to be at increased risk of premature OA, and the reasons for this are not clear. Total joint arthroplasty is usually successful in these patients, thus referral is appropriate.[71]

Every child with OI benefits from appropriate rehabilitative therapy.[72] Bracing with lightweight plastics while the child begins to walk can minimize microfracture and bowing of the upper femurs. Muscle-strengthening exercises are essential as primary care and after immobilization for fracture. Perhaps the most beneficial programs have been

developed around swimming, preferably in heated pools, and as part of continuous rehabilitative medical care.

EHLERS-DANLOS SYNDROME

The heterogenous group of disorders grouped together as Ehlers-Danlos syndrome (EDS) illustrates the genetic and clinical variability characteristic of the heritable disorders of connective tissue. The most cardinal feature of these disorders is the presence of joint hypermobility, associated with an increase in skin elasticity and skin fragility. There are more than 10 recognized types of EDS, and in 1997, a simplified classification was proposed, dividing EDS into six major clinical types. The classification includes the types of classic, hypermobility, vascular, kyphoscoliosis type, arthrochalasia, and dermosparasix, and several rarer EDS types, grouped into "other forms."[73] However, clinically EDS can be difficult to separate because of considerable overlap in phenotype findings.

Ehlers-Danlos Syndrome (Classic Type)

Clinical Features

This autosomal dominant type of EDS accounts for approximately 80% of the reported cases[74] and is inherited as an autosomal dominant trait. Originally, EDS was classified as types I and II, and now they are classified as the classic form, although these subclassifications are still in use by some clinicians. Previously, they were distinguished from each other based on joint laxity and skin fragility, which are less severe than in type II EDS. Most prototypic forms of EDS are characterized by varying degrees of hyperextensibility of large and small joints and are classic findings in EDS. Thus it is critical that hyperextensibility be defined, and differentiating mild "normal" laxity from hyperextensibility can be challenging. Beighton has presented a clinically useful classification of joint laxity.[74]

1. Passive dorsiflexion of the fifth digit beyond 90 degrees = one point for each hand
2. Passive apposition of the thumbs to the flexor surface of the radius = one point for each hand
3. Hyperextension of the elbows beyond 10 degrees = one point for each side
4. Hyperextension of the knees beyond 10 degrees = one point for each knee
5. Flexion of the trunk forward so that the palms are placed flat on the ground = one point

A score of five or more points is defined as joint hypermobility.

Large-joint hyperextensibility is seen in varying degrees in the classic form and decreases with age. Recurrent joint dislocations, periodic joint effusion related to trauma, and the eventual appearance of OA pose significant management problems. Bilateral synovial thickening has been observed in EDS, along with the accumulation of small masses of crystalline material in synovial villi. It was observed that patients with EDS constituted 5% of cases in a pediatric arthritis clinic population.[75] There is debate about whether affected infants may be born prematurely to affected mothers because of early rupture of amniotic membranes.[76] Patients with EDS have characteristic facies, with a broad nasal root and epicanthal folds. They may have large, lax ears, and traction on the ears or elbows reveals skin hyperextensibility. Another sign of hypermobility is the ability to touch the tip of the tongue to the nose (Gorlin's sign).[77,78] In addition, absence of the lingual frenulum is characteristic for this disorder.[77]

In EDS the skin has a characteristic soft or "velvety" feel that can be appreciated by stroking of the forearms. Thin, atrophic corrugated and hyperpigmented scars are found on the forehead, under the chin, and on the lower extremities (known as *cigarette paper* or *papyraceous* scars), although this is not a uniform finding. Typically, skin lesions heal slowly after injury or surgery. Molluscoid pseudotumors (violaceous subcutaneous tumors ranging in size from 0.5 to 3 cm) may be palpated in tissue over pressure points on the forearms and lower extremities and may be seen on radiographs. Although many patients claim to bruise easily, ecchymoses distributed on the extremities are found only in patients with the more severe forms of the disorder. Severe bilateral varicose veins are a common problem.

Associated pulmonary complications of EDS include spontaneous pneumothorax, pneumomediastinum, and subpleural blebs.[79] Mitral valve prolapse and tricuspid valve insufficiency may complicate the classic EDS, and aortic root dilatation has been reported, although the rate of progression is unknown.[80,81] The spectrum of skeletal abnormalities include thoracolumbar kyphoscoliosis, a long, giraffe-like neck, downward sloping of the ribs of the upper part of the thorax, and a tendency toward reversal of the normal cervical, thoracic, and lumbar curves. Anterior wedging of thoracic vertebral bodies occasionally is seen.

Ehlers-Danlos Syndrome (Hypermobility Type)

The hypermobile type of EDS is a dominantly inherited disorder that presents as marked joint and spine hypermobility, recurrent joint dislocations, and the typical soft skin that is neither hyperextensible nor velvety. Individuals with EDS III may have virtually normal skin. Because of the extent of joint laxity affecting both large and small joints, these patients experience multiple dislocations and may require surgical repair. The shoulders, patellae, and temporomandibular joints are frequently sites of dislocation. Musculoskeletal pain may mimic that of the fibromyalgia syndrome, and patients frequently seek medical attention for symptoms consistent with chronic pain.

One of the difficulties in this subtype is differentiating it from benign hypermobility syndrome. Benign hypermobility syndrome was used to describe patients with generalized joint laxity, associated musculoskeletal complaints, but normal skin.[82] They do not have the classic stigmata of either EDS or Marfan syndrome. Many of these patients are seen in their twenties and thirties with rheumatologic symptoms that can pose problems in diagnosis and treatment. The precise approach and treatment for these patients is not clear.

Structural and Molecular Pathology of the Classic and Hypermobile Type of Ehlers-Danlos Syndrome

Abnormally large, small, or frayed dermal collagen fibrils and disordered elastic fibers have been observed in the classic and hypermobile forms of EDS by electromicroscopy.[83]

Type V collagen is a heterotrimeric collagen composed of the products of three genes: *COL5A(V)*, *COL5A(V)*, and *COL5A(V)*. Type V collagen may stabilize type I collagen by co-assembling with that protein. It has been established that approximately 50% of patients with either the classic or hypermobility types of EDS have mutations in *COL5A1(V)* or *COL5A2(V)*.[84] Furthermore, in some cases of EDS classic type a heterozygosity for mutations in *COL1A1* has been seen.[85]

Ehlers-Danlos Syndrome (Vascular Type)

This autosomal dominant disorder is one of the most severe forms of EDS and was formerly referred to as *EDS type IV*. It is associated with arterial rupture, commonly involving iliac, splenic, renal arteries, or the aorta, and resulting in either massive hematomas or death.[86] Arterial rupture may lead to stroke or intracompartmental bleeding in a limb. Patients with this disorder are also susceptible to rupture of internal viscera and may experience repeated rupture of diverticula on the antimesenteric border of the large bowel. Problems with pregnancy vary from pre-term delivery to uterine or vascular rupture, although delivery is uneventful in many instances.[87,88] Typical causes of death in families with EDS have included gastrointestinal rupture, peripartum uterine rupture, rupture of the hepatic artery, and vascular ruptures.

In contrast to the other forms of EDS, EDS IV is not associated with hyperextensibility of large joints, although small joints may be minimally hypermobile. These patients have thin, soft, transparent skin, through which a prominent venous pattern is seen, especially on their chest walls. Their skin is not "doughy" as in the classic form. Excessive bruisability may occur. Vascular EDS includes, as a subgroup, patients who have been described as *acrogyric*. These individuals have characteristic thin faces, prominent eyes, and extremities that lack subcutaneous fat, giving the appearance of premature aging. Peripheral joint contractures and acro-osteolysis have been described.[89] Spontaneous hemopneumothorax associated with hemoptysis and mitral valve prolapse occurs frequently.[90] Surgical repair of ruptured vessels or internal viscera is extremely difficult because of friable tissues. Anesthetic and surgical difficulties related to intubation, spontaneous arterial bleeding during surgery, and the ligation of vessels that tear under pressure complicate surgical maneuvers. Similarly, arteriography may be dangerous in these patients. These patients can be quite difficult to manage. Imaging studies may reveal normal-appearing aorta or other large vessels that rupture shortly after a "normal study."

Molecular Pathology

Although EDS IV was clinically recognized as a disorder distinct from the other forms of EDS, the finding that tissues from these individuals were deficient in type III collagen clearly distinguished this as a separate form of EDS. Type III collagen is a homotrimer (1[III]3) found in skin, blood vessels, and the walls of hollow viscera. Heterozygosity for mutations in the gene encoding *COL3A1* leads to EDS vascular type and affects both the synthesis and secretion of type III collagen.[90-92] Various types of mutations have been identified, including missense, nonsense, and deletions, and there is no correlation between the clinical phenotype and type of type III collagen mutation. In this disorder biochemical abnormalities include decreased production of type III collagen or production of an abnormal homotrimer that is retained in the endoplasmic reticulum and, if secreted, contributes an an abnormal extra-cellular matrix. Biochemical and mutational analysis for this disorder is available. Optimal surveillance of these patients, particularly for vascular adverse events, has not been determined.

Therapy in the Classic, Hypermobility, and Vascular Types of Ehlers-Danlos Syndrome

There are no specific treatments for these forms of EDS. Supportive therapy, however, is essential for preservation of normal joint function and alleviation of joint pain. Planned exercise programs and muscle-strengthening exercises are useful and do much to maintain a positive outlook in these individuals, who may have a poor prognosis if joint stability and articular surfaces are compromised by excessive activity or chronic trauma. Unfortunately, many children and young adults with large joint hypermobility are attracted to activities such as gymnastics and dance, and these activities promote hypermobility and joint damage. The presence of multiple ecchymoses raises concern about a bleeding diathesis, particularly at the time of elective surgery. Although no consistent basis exists for the hemorrhagic tendency in the classic and hyperextensibility forms of EDS, anecdotally these patients tend to have higher blood losses than expected at surgery. In our center, we discourage pregnancy in patients with the vascular form, because the mortality rate is increased.

Arthrochalasia Type

Formerly known as *EDS VIIA* and *VIIB*, this is an another autosomal dominant form of EDS resulting from mutations that cause faulty processing of type I collagen at the N-terminus.[93,94] EDS, arthrochalasia type, is characterized by pronounced and generalized joint hypermobility, moderate cutaneous elasticity, moderate bruising, a characteristic round facies with midface hypoplasia, and significant short stature. Their skin has a doughy feel and is fragile and hyperelastic. Kyphoscoliosis and muscle hypotonia are frequently present. These patients experience multiple dislocations, particularly involving large joints, including the hips, knees, and ankles. These dislocations often present in the newborn period, especially at the hips and ankles. Patients frequently need orthopedic surgery for their joint dislocation, and their tissues are highly friable, which complicates orthopedic procedures.

Molecular Pathology

The two disorders (EDS VIIA and EDS VIIB), termed *arthrochalasia type*, result from mutations involving the N-terminal propeptide cleavage site of type I collagen. The arthrochalasia type of EDS has provided insight into the process of normal type I collagen fiber formation. The initial observation was of an accumulation of unprocessed

procollagen within the dermis of affected individuals.[95] With subsequent recognition that procollagen has both N- and C-terminal extension propeptides and that separate enzymes are responsible for their removal, the syndrome became more sharply defined as an accumulation of procollagen with the N-terminal peptides still attached (pN collagen).[96] Of the two distinctly different genetic abnormalities resulting in procollagen accumulation, the more frequent form is the mutational resistance of a procollagen cleavage site to the action of the N-terminal procollagen peptidase. The resistance results from an amino-acid substitution or deletion in the proCOL1A1 or pro2COL2A1chain (type VIIA and VIIB, respectively), leading to a portion of the collagen chains containing an abnormal N-terminal extension. This results from mutations in *COL1A1* or *COL1A2* in exon 6 of the molecule, which alters the proteinase cleavage site. Those individuals with mutations in exon 6 of *COL1A1* are more severely affected than those with similar mutations in *COL1A2*.

Ehlers-Danlos Syndrome (Dermatosparaxis Type)

This type, dermosparaxix type, was formerly known as *EDS VIIC* and is an autosomal recessive form of EDS. In this type, the skin is extremely fragile, soft, and doughy, with easy bruising. The phenotype includes blue sclerae, marked joint hypermobility, micrognathia, large umbilical hernia, epiphyseal delay, and mild hirsuitism.[93] The dermosparaxix type results from a deficiency of the procollagen-N-propeptidase, in contrast to the arthrochalastic form, which involves the enzyme cleavage site and individuals have been identified who are homozygous form mutations in the gene,. Interestingly, this defect is homologous to the defect in sheep and cattle termed *dermatosparaxis*.[97]

Ehlers-Danlos Syndrome (Kyphoscoliosis Type)

This type of EDS, kyphoscoliosis type, formerly known as *EDS VI*, is inherited as an autosomal recessive disease. The findings in this disorder include severe kyphoscoliosis, noted-at-birth recurrent joint dislocations, hyperextensible skin and joints, poor tone, and reduced muscle mass.[98] The skin is grossly abnormal, and has been described as pale, translucent, velvety and, upon trauma, showing gaping wounds that heal poorly. One difference in this form of EDS is that there is significant ocular involvement. Affected individuals have microcornea, retinal detachment, and glaucoma leading to blindness in some individuals. In addition, respiratory and cardiac compromise and, ultimately, cardiorespiratory failure may develop in patients with severe kyphoscoliosis.

Molecular Pathology

This disorder results from lysyl hydroxylase deficiency.[99] A variety of mutations within the lysyl hydroxylase gene have been defined and include premature stop codons, amino-acid substitutions, internal deletions, and compound heterozygotes.[99] Defective lysyl hydroxylase impairs the conversion of lysyl residues to hydroxylysine on procollagen peptides. The consequence of deficient hydroxylysine content of collagen is the effect it has on cross-linking, which helps stabilize the mature collagen molecule.

Other Ehlers-Danlos Syndrome Types

There are numerous other rare forms of EDS that have some overlap with other disorders or have only been reported in a small cohort of individuals, and thus will not be included in the discussion.

MARFAN SYNDROME

One of the most common inherited disorders of connective tissue, Marfan syndrome (MFS) is an autosomal dominant disorder with a reported incidence of 1 in 10,000 to 20,000 individuals.[100] There is a wide spectrum of clinical presentations, from the severe infantile form to individuals who are only mildly affected. Although the most impressive findings are relative to the musculoskeletal, cardiac, and ocular findings, affected individuals also suffer from pulmonary, neurologic, and psychological complications. Marfan syndrome has also become one of the few genetic disorders for which there has been advocacy for treatment to slow the progression of the disease. Physicians need to recognize the phenotype because many of the affected individuals are seen with life-threatening emergencies.

Clinical Features

Marfan syndrome can be difficult to diagnose in some individuals and families, and it also has been recognized that it has been overdiagnosed. Stringent criteria for this diagnosis were proposed in 1996 and revised in 2010.[100] The 1996 criteria rely on the recognition of both "major" and "minor" clinical manifestations involving the skeletal, cardiovascular, dura, and ocular systems. Major criteria include four of eight typical skeletal manifestation and ectopia lentis, aortic root dilatation involving the sinuses of Valsalva or aortic dissection, and lumbosacral dural ectasia by computed tomography (CT) or MRI. Major criteria for establishing the diagnosis in a family member include having a parent, child, or sibling who meets a major criterion independently, the presence of a *FBN1* mutation. To unequivocally establish the diagnosis in the absence of a family history requires a major manifestation from two systems and involvement of a third system. If a mutation known to cause MFS is identified, the diagnosis requires one major criterion and involvement of a second organ system. The reason for this is that there is a great deal of intrafamilial variability in this disorder, and there are individuals who harbor heterozygosity for mutations, yet do not meet criteria for Marfan syndrome and may have different prognoses.[101] Similar to other connective tissue disorders, there is wide variability in phenotypic expression.

Aortic disease leading to the formation of aneurismal dilatation and dissection is the main cause of morbidity and mortality in the MFS.[101] Dilatation of the aorta is found in 50% of children and progresses with time. Echocardiography demonstrates that 60% to 80% of adult patients have dilatation of the aortic root that may involve other segments of the thoracic aorta, the abdominal aorta, or even

the carotid and intracranial arteries. Dissection usually begins above the coronary ostia and extends the entire length of the aorta. Of patients with MFS, 60% to 70% have mitral valve prolapse with regurgitation. Heart failure and myocardial infarction may complicate the course of patients with MSF. Pregnant women are at particular risk for aortic dissection, particularly those who already have aortic root dilatation; this should be taken into consideration when treating women of reproductive age with MFS.[102]

Arachnodactyly occurs in 90% of patients. Listed below are techniques that aid in determining arachnodactyly.

- The thumb. The Steinberg test is positive when the thumb, enclosed in the clenched fist, extends beyond the hypothenar border.
- The wrist. The Walker-Murdoch sign is positive when there is overlap of the thumb and fifth digit when they encircle the opposite wrist.
- The metacarpal. The metacarpal index is done by radiographic determination and is the mean value of the lengths divided by the midpoint widths of the second, third, and fourth metacarpals. In healthy patients, the metacarpal index ranges from 5.4 to 7.9, whereas this range is 8.4 to 10.4 in patients with MFS.

Thoracic kyphosis may be associated with reduced lung capacity and residual volume that may lead to pulmonary insufficiency. Dural ectasia, which may occur in as many as 40% of patients, results from enlargement of the spinal canal caused by progressive ectasia of the dura and neural foramina and erosion of vertebral bone. This usually involves the lower spine.[103] Diminished BMD has been reported in several patients with MFS.[104] Ectopia lentis occurs in 50% to 80% of patients with MFS. Subluxation of the lens is usually bilateral and appears by the age of 5 years. Although the lens is typically displaced upward, displacement into any quadrant may occur. Visual acuity is diminished in many patients because of lens subluxation or secondary acute glaucoma. Secondary myopia, retinal detachment, and iritis with loss of vision contribute to most of the ocular-related morbidity.[105]

Large epidural venous plexuses in the lumbar and cervical regions have been found to develop in patients with MFS, a major diagnostic criterion for the syndrome. These engorged venous plexuses, which are visualized by MRI myelography have, in turn, been associated with the syndrome of spontaneous intracranial hypotension, which is also associated with dural tears. Clinical signs of this are severe headache, back and leg pain, radiculopathies, and incontinence secondary to cerebral displacement. Spinal abnormalities in MFS include increased interpedicle distance of nonrotated vertebrae, vertebral inversion (flattening of the normal kyphosis at the dorsal level and kyphosis or disappearance of the physiologic lordosis at the lumbar level), and vertebral dysplasia (dolichospondylia, elongated vertebral bodies with increased concavity). Scoliosis constitutes one of the major management problems in MFS. In one series, the average age of onset was 10.5 years (range of 3 to 15 years), with rapid progression during adolescence. If mechanical bracing or physical therapy fails to halt progression, spinal fusion should be considered, particularly when the curvature exceeds 45 to 50 degrees.[106,107]

Differential Diagnosis

Homocystinuria

Homocystinuria, which shares several skeletal and ocular features with MFS, is the prime diagnostic consideration.[108] This is an autosomal recessive disease. The characteristic features of this metabolic disorder of sulfur metabolism are marfanoid phenotype with joint laxity, scoliosis, lens dislocation, early-onset osteoporosis, vascular thrombosis affecting arteries and veins due to increased clotting activity and the cytotoxic effect of homocysteine on vascular endothelial cells, and mild mental retardation.[108]

Cystathionine β-synthase (CBS) deficiency is the most common cause of homocystinuria.[108] Affected individuals have elevated levels of homocystine and methionine levels, whereas cystathionine and cysteine levels in blood are decreased. Importantly, this disorder is differentiated from MFS because the direction of ectopia lentis is different than MFS and there is no progressive aortic root dilation.

Molecular Biology of Marfan Syndrome

Fibrillin 1 (FBN1) protein is an important component of both elastic and nonelastic connective tissues throughout the body.[109] It is the main protein of a group of connective tissue microfibrils that are essential for normal elastic fibrillogenesis. In nonelastic tissues, the FBN1-containing microfibril functions as an anchoring fiber. *FBN1* is a large gene (65 exons).

FBN1 mutations occur across a wide range of milder phenotypes that overlap the classic Marfan phenotype, including dominantly inherited ectopia lentis, Shprintzen-Goldberg syndrome, acromicric dysplasia, Weill-Marchesani syndrome, and familial or isolated forms of aortic aneurysms.[110-115] The majority of these are private mutations (occur genetically independent with no "hot spot" in the molecule). The one exception is the rare infantile MFS mutations, which cluster between exons 24 and 26 and exon 32.[116] Heterozygosity for missense, frameshifts, deletions and insertions, splice site alterations, and nonsense mutations have all been seen.[117] The clinical presentation of the fibrillinopathies caused by *FBN1* mutations range from isolated ectopia lentis, to short stature in acromicric dysplasia, to severe neonatal MFS, which generally leads to death within the first 2 years of life

Treatment

In 1972, the life span of untreated patients with classic MFS was approximately 32 years. The early mortality in the MFS results primarily from complications associated with aortic dilatation. This symmetric dilatation of the sinuses of Valsalva is progressive throughout life and is often detectable in infancy. In the early 1970s, it was suggested that perhaps treatment and surveillance could lessen the complications of aortic dissection in MFS. There have been many treatment trials with β-blockers. When compared with the control group, the treated individuals had a significantly slower rate of dilatation of the aortic root, improved survival, and fewer treated patients reached a clinical end point (death, congestive heart failure, aortic regurgitation, aortic dissection, or cardiovascular surgery).[118,119]

Data generated from mouse models of MFS suggest excessive signaling by the transforming growth factor (TGF)-β family of cytokines.[120] A large randomized control trial on these findings suggested that losartan, an antihypertensive, and an angiotensin II blocker would have advantages over β-blocker use because it can attenuate TGF-β signaling. A randomized control study in MFS using atenolol versus losartan did not show any difference between the two drugs.[121]

Echocardiograms are the mainstay of management for the aortic root complications of MFS. Elective repair of aortic root disease before enlargement to 4.5 cm is typically suggested and is preferable to emergency repair required for marked dilatation or dissection.[122] Mitral valve replacement is frequently accomplished during the same procedure. Most importantly, repeated trials have shown that patients who undergo elective repair versus emergent repair do substantially better.

Correction of scoliosis may be attempted with bracing; however, surgical repair should be considered when the curve exceeds 40 degrees. Progressive scoliosis in MFS may require fixation with rods, and complications of joint laxity may require orthopedic correction. Arthropathy associated with excessive joint mobility may require orthopedic intervention. Dislocated lenses should not be removed surgically unless more conventional means of correcting vision are ineffective.

LOEYS-DIETZ SYNDROME

In 2005, individuals with a previously undescribed autosomal dominant aortic aneurysm syndrome were described.[123] This disorder, now referred to as *Loeys-Dietz syndrome*, is also characterized by hypertelorism, bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection. Other abnormal findings include craniosynostosis, structural brain abnormalities, mental retardation, congenital heart disease, and aneurysms with dissection throughout the arterial tree.

Some individuals with Loeys-Dietz syndrome have a clinical phenotype that overlaps with MFS, but none met diagnostic criteria set forth. Although MFS is associated with progressive arterial disease, in Loeys-Dietz syndrome, the aneurysms tend to be particularly aggressive and rupture at an earlier stage and size than seen in MFS.[123] Heterozygosity for mutations in *TGFBR1*, *TGFBR2*, *TGFB2*, and *SMAD3* have been identified.[123-125] From a management perspective, it is important to recognize these individuals because they are managed more aggressively than in MFS.[126] Aortic aneurysms are corrected at smaller sizes (4 cm), and complaints such as abdominal pain and headaches should be thoroughly investigated because they may be associated with aneurysms. The distinction from MFS is important because the management needs to be even more aggressive.

CONGENITAL CONTRACTURAL ARACHNODACTYLY

Congenital contractural arachnodactyly is an autosomal dominant condition that includes tall stature, arachnodactyly, dolichostenomelia, and multiple contractures involving large joints.[127] There is a characteristic "crumpled ear" deformity caused by a flattened helix with partial obliteration of the concha. Marked deformity of the chest cage also occurs, and scoliosis may be progressive and severe. For unknown reasons, the contractures tend to become less severe with age. Radiographically, osteopenia can be seen. The ocular and typical cardiac lesions of classic MFS are absent. This disorders result from heterozygosity for mutation in *FBN2*.[127]

CONCLUSION

The heritable disorders of connective tissues are a heterogenous group of disorders characterized by abnormalities in skeletal tissues, which include cartilage, bone, tendon, ligament, muscle and skin. They are fascinating because the clinical spectrum ranges from extreme short stature to excessively tall individuals, and the types of altered genes span all numerous gene families and pathways. Affected individuals usually need medical attention their entire lives and, unfortunately, have been victims of appearing different because they cannot mask their abnormalities. Understanding and appreciation for the unique set of medical issues in each disorder will hopefully improve these individuals' quality of life and their life span.


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