# General Skeletal Disorders

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## Osteogenesis Imperfecta Background

Descriptions of osteogenesis imperfecta (OI) date back to Egypt from 1000 BC, when a mummy was characterized as having a wormian skull bone, amber-colored teeth, and bowed legs [1]. Olaus Jakob Ekman provided the first scientific description of OI in 1788; however, the first use of the phrase "osteogenesis imperfecta" to describe the condition was by Willem Vrolik in 1849 [1, 2]. Since then, numerous other names have been used to describe OI: mollities ossium, fragilitas ossium, osteopsathyrosis idiopathica, osteoporosis fetalis, osteomalacia congenital, Lobstein's disease, Vrolik's disease, Eddome syndrome, and van der Hoeve syndrome [1, 3].

## Genetics

OI is characterized as a heterogeneous group of inherited disorders caused by mutations in genes that code for type I procollagen (COL1A1 and COL1A2) [1]. These genes are found on chromosomes 7 and 17, respectively [4], and 286 mutations of type I collagen have already been described [3]. The mutations of type I procollagen account for approximately 90 % of all cases of OI [2] with the majority of these cases inherited in an autosomal dominant fashion or caused by a sporadic mutation [4]. More recently, research has identified eight other genes associated with a portion of the remaining 10 % of OI cases. These are autosomal recessive in inheritance and all but two affect type I collagen by encoding proteins involved in the biosynthesis of type I procollagen. Cartilage-associated protein (CRTAP), LEPRE, PPIB, SERPINH1, and FKBP10 indirectly alter type I collagen synthesis, while SP7, and SERPINF1 do not [2].

## Classification/Characterization

Multiple classification systems have been devised to characterize the varying degrees of phenotypic penetrance displayed by OI. Initially categorized by Looser in 1906 as whether fractures were present at birth (congenital) or after birth (tarda), Seedorff expanded on this in 1949 to include fractures within the first year of life (tarda gravis) or after the first year of life (tarda levis) [3]. In 1985, Frederic Shapiro further divided the congenital and tarda into type A and B depending on the timing of initial fracture and the radiographic appearance of the bones at initial fracture. Congenita A is classified as in utero/at birth with crumpled femurs and ribs and congenita B has normal bone contour. Tarda A is classified as fractures before walking age and tarda B is fractures after walking age [3]. The classification system of Sillence, from 1979, is still the most widely used system and was initially broken up into four types. Type I is the mildest form, is autosomal dominant and is broken up into type A (without dentinogenesis imperfecta) and type B (with dentinogenesis imperfecta). Patients will have blue sclera and a normal life expectancy. Type II is inherited in an autosomal recessive pattern and is lethal (primarily from respiratory failure, intracranial hemorrhage, or brainstem compression). Type III is a severe, autosomal dominant or recessive inheritance, and typically presents with normal sclerae and fractures around birth that can result in progressive deformity.

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D.R. Laub Jr. (ed.), *Congenital Anomalies of the Upper Extremity: Etiology and Management*,
DOI 10.1007/978-1-4899-7504-1_26, © Springer Science+Business Media New York 2015

Type IV is of intermediate severity, has an autosomal dominant inheritance, and has significant phenotypic variation [1, 3]. The initial Sillence classification system has since been expanded to include patients who do not have a collagen mutation. Type V is autosomal dominant, has hypertrophic callus development after fracture, and can have calcification of the interosseous membranes that can limit pronation and supination and lead to radial head dislocation. Type VI is autosomal recessive, has moderate to severe skeletal deformity and fractures and does not respond as well to bisphosphonate therapy. Type VII is autosomal recessive and has moderate to severe skeletal deformity that includes coax vara and rhizomelic limb shortening [3, 5].

## Management

Operative and non-operative/medical management of OI is for symptomatic treatment only and is not curative and includes a multidisciplinary team effort to improve function, minimize disability, and maximize mobility status and quality of life [1]. Various different systemic medical therapy strategies have been attempted and include calcitonin, sodium fluoride, calcium anabolic steroids, growth hormone, magnesium oxide, vitamin C, and vitamin D, all of which have had mixed results [1]. Bisphosphonates are the only medical management option for OI that has been shown to have a beneficial effect and is now considered the standard of care [4, 5]. The nitrogen-containing bisphosphonates inhibits protein prenylation and guanosine triphosphatase formation, which results in osteoclast apoptosis [3], and this ultimately results in increased cortical thickness and bone mineral density [4]. In addition to this, decreased chronic bone pain, improved ambulation scores, decreased fracture rates, increased vertebral height, and improved grip strength (with pamidronate therapy) have also been seen in the initial 6 weeks after bisphosphonate therapy [3, 4]. Cyclical intravenous pamidronate and zoledronic acid are the bisphosphonates most frequently used in patients with OI and is limited to a few years due to the unknown long-term effects of bisphosphonates [3–5]. Osteonecrosis of the jaw is associated with bisphosphonate therapy, however, no reports of OI patients have been identified and the risk of this in OI patients is currently unknown [3].

Bone marrow transplantation is another treatment option that has so far not proven to be beneficial and requires more research to determine its true efficacy. Gene therapy and stem cell therapy are other areas of research that could be beneficial for OI patients but have yet been thoroughly investigated [3, 5].

Surgical principles and goals are designed to restore the normal bone axis by correcting deformity, minimize the incidence of fracture, avoid bone bowing, and use gentle technique to preserve muscle and minimize soft tissue injury [1, 3, 4]. Plates and screws are rarely indicated for fractures in OI patients, and the standard is use of an intramedullary device. Osteotomies are also used in conjunction with internal fixation to correct significant deformity. Multiple different rod systems have been proposed for use including double Rush rods, Bailey–Dubow and Sheffield rods, and Fassier–Duval telescoping nail with the overlying theme of selecting the largest diameter rod that will pass through the medullary canal at its narrowest point [3, 4]. The Fassier–Duval nail allows a minimally invasive technique to be used, can be used on multiple long bones during the same surgical setting, and thus far has had a lower revision rate [4].

Humeral intramedullary rods with either Rush rods or Fassier–Duval nails require the device to not impinge in the shoulder, and the patient to have full range of motion at the end of the procedure. Forearm deformity can be corrected with ulnar intramedullary wires and radial osteotomy and intramedullary fixation with the latter being much more technically challenging [4].

## Marfan Syndrome

### Background

Antoine Marfan, a French pediatrician, first described the skeletal characteristics of Marfan syndrome in 1896 in a 5-year-old girl who presented a tall stature and slender digits; however, this was more likely a presentation of congenital contractural arachnodactyly [6]. Marfan further characterized features of Marfan syndrome including ectopia lentis and mitral valve disease. Ultimately, it was Victor McKusick who stated that Marfan syndrome was a connective tissue disorder that encompassed abnormalities of the cardiovascular (including aortic dissections and aortic valve pathology), ocular, and skeletal systems [6].

### Genetics

Harry Dietz discovered the genetic cause of Marfan syndrome in 1991 when he reported that a mutation in genes that code for fibrillin-1, an extracellular matrix protein, leads to classic Marfan syndrome, which is characterized as a clinically and phenotypically variable inherited disorder [6, 7]. Approximately 25 % of cases are thought to be from de novo mutations, primarily in genes for fibrillin-1, and the remaining cases are inherited in an autosomal dominant fashion [6]. FBN-1 gene, found on chromosome 15q21.1, is

the only gene known to cause classic Marfan syndrome when mutated and is present in over 90 % of Marfan syndrome patients [6, 7].

Fibrillin-1 also interacts with transforming growth factor (TGF)-β, a cytokine that influences cell proliferation, differentiation, extracellular matrix formation, cell-cycle arrest, and apoptosis. Mutations in fibrillin-1 can lead to abnormal signaling pathways via this interaction. Mutations in TGFβR1, on chromosome 9, and TGFβR2, on chromosome 3, also alter the TGF-β signaling pathway. Mutations in TGFβR2 have been identified in patients diagnosed with Marfan syndrome (termed Marfan syndrome type II), yet these patients did not have characteristic findings of Marfan syndrome. Loeys–Dietz syndrome, which has many features similar to and unique from Marfan syndrome, is characterized by mutations in either TGFβR1 or TGFβR2 [6, 7]. Dietz states that patients with mutations in TGFβR1 and TGFβR2 tend to have a more aggressive vascular disease and risk of vessel rupture than patients with classic Marfan syndrome, and due to this Loeys–Dietz syndrome, rather than Marfan syndrome type II, in order to further individualize care, counseling, and management [7].

Multiple related disorders are also caused by mutations in the FBN-1 gene and TGF-β signaling pathway including mitral valve prolapse syndrome, MASS phenotype (Mitral valve prolapse, Aortic enlargement, Skin, and Skeletal features), Familial ectopia lentis, Shprintzen–Goldberg syndrome, Weill–Marchesani syndrome, Stiff skin syndrome (TB4 of FBN-1), geleophysic dysplasia (ADAMTSL2), acromicric dysplasia (TB5 of FBN-1), Loeys–Dietz syndrome (TGFβR1 and 2), Loeys–Dietz like syndrome (SMAD3), Myhre syndrome (SMAD4), and isolated skeletal or cardiovascular features of Marfan syndrome [6–8].

## Classification/Diagnosis

The typical description of a patient with Marfan syndrome to make a clinician suspicious is a patient who is thin, tall, has long slender limbs (dolichostenomelia), arachnodactyly (long, thin, hyperextensible fingers), a pectus deformity, and scoliosis [6, 9]. The Ghent nosology, a revision from the Berlin criteria, is a stricter set of diagnostic criteria including family history, personal medical history, physical exam, slit lamp evaluation, and echocardiography, used to assist in the diagnosis and treatment of Marfan syndrome [6–8]. The nosology assesses seven systems (skeletal, ocular, cardiovascular, pulmonary, skin and integument, dura, and family history) and has major (uncommon in other diseases) and minor criteria. To consider the skeletal system involved, a patient must have at least two major criteria or one major criterion and two minor criteria. Major criteria include pectus carinatum, pectus excavatum requiring surgery, scoliosis >20° or spondylolisthesis, medial displacement of the medial malleolus causing pes planus, protrusio acetabuli, reduced upper-to-lower segment ratio or arm span-to-height ratio >1.05, positive wrist and thumb signs, and reduced extension at the elbows (<170°). A minor criterion is joint hypermobility/laxity, which can lead to contractures, particularly of the fingers and elbows [6]. While it has been shown that patients with Marfan syndrome have a decreased bone mineral density, there is no difference in their risk for fracture [6].

The wrist and thumb signs are used to evaluate arachnodactyly. The wrist sign/test (aka Walker–Murdoch) is positive when the patient wraps their fingers around their contralateral wrist and their thumb overlaps the distal phalanx of their small finger. The thumb sign/test is positive when the patient grips their thumb in their palm and the entire nail of the thumb projects beyond the ulnar border of the hand [6–9].

## Management

Treatment options for patients with Marfan syndrome require a multidisciplinary team effort including geneticist, cardiologist and cardiothoracic surgeons, ophthalmologist, and an orthopedist [7]. The upper extremity manifestations usually require no treatment unless contractures become symptomatic after which time, conservative management may be initiated [10]. This includes physical therapy and bracing for elbow and finger contractures. The hyperlaxity seen in Marfan patients typically requires no treatment; however, it may predispose them to easier dislocation. In certain circumstances, capsular reconstruction has been required to reduce pain and restore function [11]. Ultimately, it is the responsibility of all providers to ensure that appropriate referrals have been made to the aforementioned specialists if there is any clinical suspicion for Marfan syndrome.

# Achondroplasia

## Background

Disproportionate short stature, macrocephaly, depressed nasal bridge, foramen magnum stenosis, thoracolumbar kyphosis, spinal stenosis, prominent buttocks, protuberant abdomen, genu varum, possible radial head dislocation, and trident hands characterize achondroplasia. Jules Parrot first used the term achondroplasia, which means "without

cartilage formation," in 1878 to help distinguish patients with achondroplasia (disproportionate short stature) from patients with rickets (proportionate short stature), although it was the art from Egypt, Greece, and Rome that first depicted examples of achondroplastic patients [12–14].

## Genetics

Achondroplasia is inherited in an autosomal dominant fashion and is part of a spectrum of disorders caused by different mutations in the genes encoding fibroblast growth factor receptor 3 (FGFR3). This gene is found on chromosome 4p16.3 and this receptor is expressed in articular chondrocytes [15]. Other disorders caused by FGFR3 mutations include hypochondroplasia, severe achondroplasia with developmental delay and acanthosis nigricans, and two types of thanatophoric dysplasia [13]. Approximately 80 % of cases are due to sporadic mutations and increased paternal age has been associated with an increased risk of new mutation [14, 15].

## Classification/Characterization

Most features of achondroplasia can be traced back to the effect of increased FGFR3 signaling on endochondral bone growth [13]. These features are quite distinct, can present at different stages of life, and are typically recognized clinically or radiographically rather than via DNA analysis; however, approximately 20 % of patients go unrecognized at birth [12–14]. Third trimester prenatal ultrasound can identify short limbs in the 3rd percentile or less, head circumference greater than the 95th percentile, and a low nasal bridge [12, 14, 15]. At birth, short stature, rhizomelic limb shortening, and characteristic facial features (frontal bossing, midface hypoplasia) are evident. In addition, certain joints may be hypermobile, primarily the knees and hands, yet contractures of the elbows and hips can also be present [12–15]. In infancy, patients have normal mental development, although motor development is typically delayed secondary to muscular hypotonia. Apnea symptoms from foramen magnum stenosis and thoracolumbar kyphosis become more evident as the individual grows [12, 14, 15].

In the upper extremity, the rhizomelic shortening is the result of short humeri with the fingertips only able to reach the top of the greater trochanters and consequently, individuals may be unable to reach the top of their head [14, 15]. An elbow flexion contracture can also develop and is secondary to a flexion deformity of the distal humerus. Elbow deformities may also include radial head subluxation or dislocation [14]. The hands have equal length metacarpals and digits and have extra space between the third and fourth rays. This creates three groups of digits (thumb, index and long, and ring and small) and gives the hand a trident appearance [14, 15].

## Management

A multidisciplinary team should be involved in the care of any patient with achondroplasia to improve function and positively affect their quality of life and should include but not be limited to pediatricians, pediatric and adult orthopedic surgeons (including spine surgeons), otolaryngologists, endocrinologists, and dentists. Operative and non-operative/medical management of achondroplasia is used primarily for symptomatic or cosmetic reasons. Human growth hormone has been trialed for achondroplastic children. While there is some improvement in growth rate and height, long-term follow-up results show no real benefit and it is not currently recommended worldwide for treatment of achondroplasia [12–15]. Other medical therapies that are being investigated include the use of parathyroid hormone and C-type natriuretic peptide. These could activate signaling pathways that could counteract the excessive FGFR3 signals in physes [13–15]. Physical therapy has also been suggested to assist with flexion contractures, but in general, elbow contractures and radial head subluxation/dislocations do not require any intervention since there is no functional loss [12–14].

Elective surgical limb lengthening has been used to address the short status of achondroplasia patients who average between 112 and 145 cm in height, which corresponds to 6–7 standard deviations below the average of an unaffected adult [12–15]. This process is extremely time-consuming and is still controversial. While it may have significant social and emotional effects, there is little evidence to support any functional benefit. Most of the discussion surrounding surgical limb lengthening is in reference to lower extremity lengthening. This is partially due to the fact that upper extremity length discrepancies are less common and better tolerated than lower extremity discrepancies [16]. On the other hand, there have been reports of functional limitations from upper extremity length discrepancies and treated with humeral lengthening. More recently, humeral lengthening by distraction osteogenesis with a monolateral frame has shown improved functional results when compared to circular frames [16].

Table 26.1 provides a brief description, the genetics, natural history, and treatment possibilities of these various conditions.

**Table 26.1** Dysplasias, syndromes, and certain genetic conditions and their associated upper extremity skeletal anomalies

| | *Achondroplasia* | *Hypochondroplasia* | *Pseudoachondroplasia* |
|---|---|---|---|
| Description | Rhizomelic shortening secondary to short humeri, flexion contractures from flexion deformities of distal humerus, elbow abnormalities, and trident appearance of hand [extra space between third and fourth rays]. Short stature noticeable at birth, foramen magnum stenosis, thoracolumbar kyphosis, spinal stenosis, and genu varum [14, 17] | Defective conversion of cartilage to bone. Less severe form of achondroplasia—body changes milder and often overlooked. Normal trunk length, disproportionately short arms and legs, hands and feet are broad and short. Differentiated from achondroplasia by lack of facial dysmorphism, less severe short stature, less obvious skeletal disproportion, and milder radiologic findings [17, 20] | Moderate to severe disproportionate short stature, ligamentous laxity, and progressive degenerative joint disease. Short-limb dwarfism with epiphyseal and metaphyseal involvement. Moderate brachydactyly, joint hyperextensibility in hands, restricted extension at elbows, and overall joint pain. Osteoarthritis in early adulthood [21–23] |
| | Radiographic findings: Rhizomelia, mesomelia, acromelia of extremities; brachydactyly, metacarpal metaphyseal cupping, phalangeal metaphyseal widening in hands; prominent deltoid insertion area in arms; third metacarpal shortening [18, 19] | Radiographic findings: Same as achondroplasia, but milder [18] | Radiographic findings: Brachydactyly proximally rounded and shortened metacarpals with small or cone-shaped epiphyses in hands, short phalanges, irregular metaphyses, and irregular carpals. Elbows may appear enlarged [18, 21] |
| Genetics | Autosomal dominant, fully penetrant, but 80 % of cases are sporadic. Locus—4p16.3; Gene—FGFR3; Protein—FGFR3 [14, 24] | Autosomal dominant; Locus—4p16.3; Gene—FGFR3; Protein—FGFR3 [24] | Autosomal dominant; Locus—19p12-13.1; Gene—COMP; Protein—Cartilage Oligomeric Matrix Protein (COMP) [24] |
| Natural History | Short stature is present at birth. Motor development may be delayed. Average height for adult male—131 cm (52 in.). Average height for adult female—124 cm (49 in.) [14, 25] | Same as achondroplasia, but milder [17, 20] | Normal length and facies at birth. Often presents at the onset of walking with a waddling gait. By 2 years of age, growth rate below the standard growth curve which leads to disproportionate short-limb short stature. Average adult heights: 116 cm for females and 120 cm for males [21] |
| Treatment | Growth hormone therapy. Upper extremity limb lengthening has been documented with an average arm length gain of 10.2 ± 1.25 cm. Surgical realignment may be performed as well [14, 25] | Growth hormone therapy and limb lengthening if necessary [26] | Evaluate for skeletal manifestations. Anterior/posterior radiographs of hands. Assess ligamentous laxity. Analgesics for joint pain [21] |
| | *Thanatophoric dwarfism/dysplasia type 1* | *Thanatophoric dwarfism/dysplasia type 2* | *Marfan syndrome* |
| Description | Underdevelopment of the entire skeleton, short-curve long bones, metaphyseal flaring, underdeveloped pelvic bones, flat acetabular roof, flat and underdeveloped vertebral bodies, cloverleaf skull may or may not be present [27, 28] | In TD2, long bones not as short as in TD1, nor are they bent and/or bowed. Metaphyses are flared and cupped. Flat vertebral bodies—but not as flat as TD1, almost all fetuses have cloverleaf skull. Overall, less severe bone involvement than TDI [27, 28] | Characterized by tall stature, thin habitus, long and slender digits, ligamentous laxity, arachnodactyly, and camptodactyly. Reduced upper-to-lower segment ratio. Bones are typically osteopenic and fracture often [6, 19] |
| | Radiographic findings: Generalized micromelia, long bones of extremities are short and have telephone receiver-like appearance; skeletal maturation and ossification centers are not altered on radiograph [18, 28] | Radiographic findings: Generalized micromelia, long bones of extremities are short and have telephone receiver-like appearance; skeletal maturation and ossification centers are not altered on radiograph [18, 28] | |
| Genetics | Autosomal dominant; Locus—4p16.3; Gene—FGFR3; Protein—FGFR3 [24] | | Autosomal dominant; Locus—15q21.1; Gene—FBN1; Protein—Fibrillin-1 [24] |
| Natural History | Most common type of lethal neonatal skeletal dysplasia; overall association with rhizomelic limb shortening, macrocephaly, and cloverleaf skull. Difficult to differentiate from other forms of short-limb dwarfism—most important difference is that TD has severe rib shortening, restricted lung volume, and respiratory distress leading to death within a few hours of birth. Most infants do not survive past a few hours or days due to respiratory insufficiency [27–29] | | Children taller than average for age. By adulthood, may reach 7 ft tall [19] |

(continued)

**Table 26.1** (continued)

| | *Achondroplasia* | *Hypochondroplasia* | *Pseudoachondroplasia* |
|---|---|---|---|
| Treatment | At birth, infant may require suboccipital decompression to alleviate craniocervical junction constriction. Joint contractures or joint hypermobility should be evaluated and followed [29] | | Therapy with nighttime splinting in extension is often successful for treatment of camptodactyly. More severe cases may require tendon transfer, release of volar structures and PIPJ. Surgery outcomes are unpredictable [30] |
| | *Osteogenesis imperfecta* | *Nail–Patella syndrome* | *Diastrophic dysplasia* |
| Description | Characterized by fragile bones, low bone mass, blue sclerae, dentinogenesis imperfecta, hearing loss, and scoliosis. Frequent fractures produce limb deformities. Bowing may occur without prior fracture. Non-accidental injury must be considered in differential diagnosis [3, 5, 31] | Abnormal development of tissue derived from mesenchyme. Nail dysplasia or absence and radial head dislocation may be seen in the upper extremity. Decreased muscle mass in proximal upper extremity [19, 32] | Endochondral ossification affected causing short stature from shortened limbs, progressive spinal deformities, foot deformities, frequent joint subluxation and dislocation, large joint contractures, ear pinnae deformities, and/or cleft palate. Hitchhiker thumb, shortened fingers, synostosis of the proximal interphalangeal joints, and ulnar deviation of fingers. Radial dislocation may also be seen clinically [33–35] |
| | Radiographic findings: Osteopenia, bone fractures, and bone deformities [31] | Radiographic findings: Radial head and capitellum hypoplasia, elbow dislocation [18] | Radiographic findings: Micromelia; short, thick tubular bones; epiphyseal dysplasia; metaphyseal flaring of long bones; bifid or V-shaped distal humerus, may also be pointed and hypoplastic; radial bowing; proximal radial dislocation at birth; brachydactyly and short ovoid first metacarpal; irregular carpal bones; joint dislocations [18, 33] |
| Genetics | *OI Types I–IV*: Autosomal dominant; Gene—COL1A1 or COL1A+G42; Protein—type 1 collagen | Autosomal dominant; Locus—9q34.1; Gene—LMX1B; Protein—LIM homeobox transcription factor 1 [24] | Autosomal recessive; Locus—5q32-33; Gene—DTDST; Protein—SLC26A2 sulfate transporter [24] |
| | *OI Type V*: Autosomal dominant; Gene—unknown | | |
| | *OI Type VI*: Autosomal recessive; Gene—unknown | | |
| | *OI Type VII*: Autosomal recessive; Protein—Cartilage-associated protein [CRTAP] [24] | | |
| Natural History | More severe forms of OI may experience bone fragility and fracture in utero and/or at birth. Milder forms may remain nearly absent in adulthood. Overall, fracture incidence decreases after puberty and increases after menopause and males in their 60s [1] | Non-progressive nail dystrophy and elbow deformities. Patellae may be absent or hypoplastic [19, 32] | Diagnosis can be made through ultrasound and molecular genetic testing prenatally or clinically at birth. Normal mental status. Growth and motor capabilities greatly affected by deformities. Disproportionate dwarfism with a mean height of 130–140 cm can be seen in affected adults [36] |
| Treatment | Bisphosphonates may be used to decrease fracture frequency, improve vertebral bone density, and strengthen grip. Surgical goal is to minimize fracture frequency, restore bone axis, and avoid bowing. Long bone internal fixation in children is common via multilevel osteotomies and telescopic intramedullary nail fixation. Long-term rod revision surgery may be required [3, 4] | Patient may be followed and regularly assessed. Surgery is sometimes necessary [19, 32] | Focus on improving mobility through casting to maintain joint positioning, physiotherapy, and other forms of therapy. Cervical spinal surgery only indicated with clinical or neurophysiological evidence of spinal cord impingement—otherwise, cervical kyphosis typically spontaneously corrects. In cases of premature degenerative arthrosis, arthroplasty is indicated. Early physical therapy may prevent joint contractures [33, 35] |

(continued)

**Table 26.1** (continued)

| | *Kniest's dysplasia* | *Cleidocranial dysostosis/dysplasia* | *Niemann-Pick disease* |
|---|---|---|---|
| Description | Damage to articular and epiphyseal cartilage leading to disproportionate dwarfism. Children present with enlarged elbow and wrist joints with restricted movement, abnormal hands with long, knobby fingers. Round faces and barrel-shaped kyphotic trunk [19, 37] | Abnormal development of membranous bones such as the clavicle. Characterized by drooping shoulders, elongated neck, and shoulder adduction anteriorly. Central clavicle may be absent and a small piece of bone articulating with the acromion [26, 38] | Lipid storage disease. Previously not known to have skeletal involvement. Joint and/or limb pain has been reported as well as decreased bone mineral density [BMD] in both affected pediatric and adult patients [39] |
| | Radiographic findings: Generalized ossification delay; epiphyses becoming hypoplastic/dysplastic; cloudy effect in physeal plate in late childhood; metaphyseal flare and epiphyseal fragmentation; reduced joint space in small joints of hand [18, 37] | Radiographic findings: Multiple pseudoepiphyses of metacarpals and tapered distal phalanges in hands [18] | |
| Genetics | Autosomal dominant; Locus—12q13.1; Gene—COL2A1; Protein—type 2 collagen [24] | Autosomal dominant; Locus—6p21; Gene—RUNX2; Protein—Run related transcription factor 2 [24] | Autosomal recessive; Gene—SMPD1; Locus—p11; Protein—Acid sphingomyelinase [24, 26] |
| Natural History | Bone formation in fetus and infant most affected. Slow growth. Normal milestones and intelligence [19, 37] | Mean adult height for males is 162 cm [26] | Patients with neurological involvement do not survive beyond 3 years. Patients without neurodegeneration usually survive into late childhood or adulthood [39] |
| Treatment | UE management not well documented | Orthopedic intervention may be necessary if severe impairment or disability occurs [38] | No definitive treatment. Early intervention for low BMD such as load-bearing activities and muscle strengthening exercises. Frequent pulmonary disease and chronic fatigue must be considered [39] |
| | *Mucopolysaccharidoses* | | |
| Description | Defective endochondral and membranous growth. Presents with dysostosis multiplex—short stature, platyspondyly with anterior beaking, 'bullet-shaped' phalanges. Joint contractures and carpal tunnel syndrome are common. Osteopenia may occur in association with pathologic fractures | | |
| | MPS I H—Hurler syndrome: Carpal tunnel syndrome, joint contractures, and dysostosis multiplex | | |
| | MPS I S—Scheie syndrome: Carpal tunnel syndrome, joint contractures, and dysostosis multiplex | | |
| | MPS II—Hunter syndrome: only X-linked MPS disorder, Carpal tunnel syndrome, joint contractures, and dysostosis multiplex | | |
| | MPS IIIA-B—Sanfilippo Types A-B: Less severe than I, II, VI, and VII | | |
| | MPS IVA—Morquio Type A: severe skeletal dysplasia, joint hypermobility, and dysplastic odontoid process | | |
| | MPS IVB—Morquio Type B: severe skeletal dysplasia, joint hypermobility, and dysplastic odontoid process | | |
| | MPS VI—Maroteaux–Lamy syndrome: Carpal tunnel syndrome, joint contractures, and dysostosis multiplex | | |
| | MPS VII—Sly syndrome: Joint contractures and dysostosis multiplex [40–42] | | |
| | Radiographic findings: Coarsened long bones, shortened ulna, Madelung deformity of distal radius, shortened metacarpals with proximal tapering, and broad clavicles [42] | | |
| Genetics | Autosomal recessive; Gene—varies by type of MPS [42] | | |
| Natural History | Affected infants may appear healthy at birth. MPS presents later—timeline varies by form. Often children have short stature and some have progressive mental deterioration [19, 42] | | |
| Treatment | Carpal tunnel release and deformity correction. Bisphosphonates may be used to help increase bone density. Palliative and supportive care such as physical and occupational therapy when indicated [40–42] | | |
| | *Hereditary multiple exostoses/multiple osteocartilaginous exostoses/diaphyseal aclasia* | *Fibrodysplasia ossificans progressiva* | *Chondroectodermal dysplasia/Ellis–van Creveld syndrome* |
| Description | Multiple cartilage-capped boney protuberances, or osteochondromas, at metaphyses of long bones. Mild short stature and disproportionate short-limbs. Rarely, an enchondroma may undergo a malignant transformation into secondary chondrosarcoma. UE most commonly presents with length discrepancy between the radius and ulna—radial bowing, radial tilting, and radial head dislocation may occur [43] | Fibrous tissues, muscles, and periosteal regions undergo progressive ossification. Shortened and deformed thumbs [19] | Short stature, irregular bone growth ad structure. Polydactyly also occurs [19] |

(continued)

**Table 26.1** (continued)

| | *Achondroplasia* | *Hypochondroplasia* | *Pseudoachondroplasia* |
|---|---|---|---|
| Genetics | *HME-1*: Autosomal dominant, Locus—8q23-24.1; Gene—EXT1; Protein—Exostosin-1 | Autosomal dominant; Locus—4q27-31, 17q21-22, or 2q23-24 [19] | Autosomal recessive; Locus—4p16 [19] |
| | *HME-2*: Autosomal dominant, Locus—11p12-11; Gene—EXT2; Protein—Exostosin-2 | | |
| | *HME-3*: Autosomal dominant, Locus—19p [24] | | |
| Natural History | Numerous osteochondromas develop near growth plates. During childhood and adolescence, osteochondromas create a pseudo-growth plate and cause deformity with growth [44] | At age five, patient starts developing large ectopic osseous collections in muscular regions. These osseous collections cause severe disability and limits joint movement [19] | |
| Treatment | Growth deformity correction and removal of symptomatic osteochondromas. To manage impending or complete radial head dislocation: Ulnar collateral carpal ligament release at the wrist and radial head resection at skeletal maturity. Ulnar wrist deviations are usually asymptomatic. If not, acute and guided-growth interventions may be successful. Malignant transformation into chondrosarcoma must be resected. Typically low grade [43] | No known effective treatment. Surgery, corticosteroids, and radiotherapy have been used. Bisphosphonates have been used to decrease ectopic osseous masses but clinical benefits are not well established [45] | Surgical excision of polydactyly [30] |
| | *Ehlers Danlos syndrome (EDS)* | *Spondyloepiphyseal DYSPLASIA* | *Multiple epiphyseal dysplasia* |
| Description | Connective tissue disorder characterized by congenital joint hypermobility, skin hyperextensibility, and tissue fragility. Joint dislocations due to little to no trauma are common as is chronic limb pain. Severity varies with type of EDS [46, 47] | Short stature due to growth disorder of spine and epiphyses. Short trunk [48] | Abnormal endochondral epiphyseal ossification centers lead to short stature. Early degenerative arthritis and chondral lesions may present. Progression of the disease may atrophy muscles causing muscle fatigue and pain [49–51] |
| | | | Radiographic findings: Small, irregular, flattened epiphyses; small, irregular carpals; proximal metacarpal rounding; Brachydactyly [18, 52] |
| Genetics | Autosomal recessive; Locus—15q14; Gene—CHST14; Protein—carbohydrate sulfotransferase 14, dermatan 4-sulfotransferase [24] | Autosomal dominant; Locus—12q13.1; Gene—COL2A1; Protein—type 2 collagen [24] | Autosomal dominant; mutations in five different genes have been identified: COMP, COL9A1, COL9A2, COL9A3, and MATN3. 80 % COMP mutation, 10-20 % cannot be identified [49] |
| Natural History | May present in the first few years of life. Joint hypermobility progression [53] | Typically normal in size and proportion at birth. Osteoarthritis with progressive joint and back pain. Normal motor and cognitive milestones [54] | May present in early childhood with knee pain and delayed ossification of femoral epiphyses [49] |
| Treatment | Orthopedic intervention may be necessary with symptomatic events | Joint replacement and pain management [54] | Early Childhood intervention to minimize and/or counteract joint deformity and preserve mobility [49] |

(continued)

**Table 26.1** (continued)

| | *Metaphyseal chondrodysplasia (metaphyseal dysplasia)* | *Chondrodysplasia punctata* | *Enchondroma* |
|---|---|---|---|
| Description | Short stature; metaphyseal irregularity, normal epiphyses, normal vertebrae [55] | Neonatal epiphyseal stippling and decreased growth | Usually a solitary, benign lesion. Multiple enchondromas have increased rate of recurrence. Approximately 40 % of enchondromas occur in the hand. Primary enchondromas of the hand typically present as pathological fracture, deformity with or without pain, and swelling. Long bone enchondromas are usually asymptomatic [56, 57] |
| | Radiographic findings: Irregularity of expanded metaphyses, wide separation of epiphyses from metaphyses. Hands have shortening with metacarpal and phalangeal cupping and coning [18] | Radiographic findings: Skeletal calcifications of the epiphyses and carpals | Radiographic findings: Stippled calcifications, endosteal scalloping, cortical thinning, and medullary expansion [58, 59] |
| Genetics | McKusick—Autosomal recessive | Most common form—X-linked dominant | |
| | Schmid, Jansen, Kozlowski—Autosomal dominant [26] | | |
| Natural History | Defects may be absent or minimal at birth and develop within months or years [55] | Most affected patients die within the first year of life [26] | Malignant transformation to chondrosarcoma possible but rare—must be considered in the differential [56, 57] |
| Treatment | UE management not well documented | UE management not well documented | In absence of progressive changes, annual clinical and radiographic examination. Overall goal of surgeon is to prevent pathological fracture and remove tumor. Standardized treatment protocol for hand enchondroma is lacking. Treatment options include observation, curettage, and curettage with autogenous bone grafting or bone graft substitute. Various bone graft materials may be used to fill the bony defect post-curettage. Sassoon, et al. recommend use of an allograft or no graft to avoid donor graft site morbidity. Internal fixation may be necessary for cortical thinning and/or fracture stabilization [57, 58, 60] |
| | *Ollier's disease/enchondromatosis* | *Fibrous dysplasia* | *Camurati–Engelmann disease [progressive diaphyseal dysplasia]* |
| Description | Development of multiple benign enchondromas located in the epiphyses of bones. Commonly seen in the phalanges. Also skeletal deformities, limb length discrepancies, pain, and the potential risk for malignant changes [61–63] | Bone-forming tissue unable to produce mature lamellar bone resulting in benign fibro-osseous lesion or lesions. Pain, swelling, deformity, and/or pathological fractures are common clinical presentations [64–66] | Sclerosing bone dysplasia causing progressive thickening of the diaphyses, bone pain, muscle weakness and atrophy |
| | Radiographic findings: Broadened metaphyses, long bone bowing | Radiographic findings: Intramedullary lesion causing bone expansion limited by cortical rim. Cortical thinning without periosteal reaction [64, 66] | |
| Genetics | SP; PTHR1 and PTPN11 mutations found in a few cases only, role still unclear [24] | SP; Locus—20q13; Gene—GNAS1; Protein—guanine nucleotide-binding protein, alpha-stimulating activity subunit 1 [24] | Autosomal dominant; Locus—19q13; Gene—*TGFB1*; Protein—transforming growth factor-β1 |

(continued)

**Table 26.1** (continued)

| | *Achondroplasia* | *Hypochondroplasia* | *Pseudoachondroplasia* |
|---|---|---|---|
| Natural History | As child grows, enchondroma increases in size. Enchondroma subject to pathological fracture. Bony masses cause angular deformities and asymmetrical growth [61] | Usually presents in first three decades of life. Child may present with pain, limp, and/or pathologic fracture. Though rare, lesion may transform into either a benign or malignant tumor [64] | Most cases present in the first decade of life. Progression is slow and unpredictable. Normal life span |
| Treatment | Limb lengthening and deformity correction often with Ilizarov fixation. Observation for possible malignant transformation. Surgical excision if chondrosarcoma occurs [61, 62] | In absence of symptoms, regular radiographs and observation are indicated until satisfied that lesion is inactive. A growing child without symptoms should be seen twice yearly for clinical evaluation of range of motion, angular deformity, and limb length discrepancy. If symptomatic lesion, "conventional surgical procedures." In cases of deformity or mechanical deficit, orthopedic intervention may be necessary to remove lesion and graft defect. Internal fixation with intramedullary rods may be used. Bisphosphonate use has been reported to have successful outcomes [45, 65, 66] | NSAIDs for bone pain and physical therapy. UE management not well documented [26] |
| | *Osteopoikilosis* | *Osteopathia striata* | *Melorheostosis* |
| Description | Sclerosing bone dysplasia, usually asymptomatic, but can cause soft tissue fibrosis and joint contractures | Sclerosing bone dysplasia with linear striations in bone seen on radiograph. Typically asymptomatic | Sclerosing dysplasia with painless, soft-tissue contractures. Linear hyperostosis progresses slowly |
| | Radiographic findings: Well defined, bilateral osteosclerotic nodules located in metaphyses and epiphyses of long bones, carpus, and scapulae | Radiographic findings: Dense linear striations seen in tubular and flat bones | Radiographic findings: Asymmetrical bands of sclerosis, described as "molten wax flowing down the side of a candle." Location varies with age—endosteal in children, extracortical, subperiosteal in adults. Hyperostosis patches seen in carpals |
| Genetics | Autosomal dominant | Autosomal dominant | Non-hereditary |
| Natural History | Presents during childhood. Children reach normal stature | | Presents by age 6 with joint contractures |
| Treatment | UE management for joint contractures and fibrosis if necessary [26] | Treatment unnecessary [26] | NSAIDs for pain. Lengthening, realigning, and contracture correction have been carried out successfully with the Ilizarov technique but with frequent complications [26] |
| | *Pyknodysostosis* | *Gorham disease/idiopathic osteolysis/disappearing bone disease* | *Dyschondrosteosis (Leri–Weill syndrome)* |
| Description | Failure of bone resorption leads to mild short stature and numerous skeletal deformities including pectus excavatum | Massive osteolysis originating from one bone may progressively involve adjacent bones. Resorbed bone is replaced by fibrous tissue | Mild mesomelic short stature. Forearm deformities, notably in the distal radius causing a Madelung deformity |
| | | Radiographic findings: Intramedullary and subcortical radiolucent foci. Foci progressively merge | Radiographic findings: Madelung deformity, humeral head hypoplasia |
| Genetics | Autosomal recessive | Non-hereditary | Autosomal dominant; Gene—*SHOX* |
| Natural History | | Often presents in second and third decades of life | Short stature, forearm and/or wrist deformity, pain typically develops by 8 years of age. Adult heights range from 135 to 170 cm |
| Treatment | Growth hormone therapy to increase stature [26] | Surgery with or without radiation therapy has shown some success, but not consistently [26] | Growth hormone has been successful in some. If wrist pain occurs, use splint and anti-inflammatories. If wrist continue to be symptomatic, reconstruction may be necessary via double osteotomy of the distal radius and ulnar recession [26] |

(continued)

**Table 26.1** (continued)

| | *Larsen syndrome* | *Gaucher's disease* | *Craniocarpotarsal dysplasia/Freeman-Sheldon/"Whistling Face" syndrome/distal arthrogryposis Type II* |
|---|---|---|---|
| Description | Hypertelorism, multiple joint dislocations, focal bone deformities. Wide distal phalanx of thumb, no distal tapering of fingers, and hypotonia may be seen<br>Radiographic findings: Accessory ossification centers in the carpals and shortened metacarpals | Lysosomal storage disorder that causes bone pain, osteomyelitis, osteopenia, pathologic fractures, and osteonecrosis. Bone crises are common | The hands have same deformity as distal arthrogryposis. Joint contractures, elbow flexion deformities, limited range of motion in shoulder |
| Genetics | Both an autosomal dominant form and an autosomal recessive form | Autosomal recessive; Locus—p1; Protein—glucocerebrosidase | Typically sporadic. Some evidence of autosomal dominant and autosomal recessive inheritance patterns |
| Natural History | | Age of presentation varies by type. Mean age at diagnosis—25 years | Presents in the first decade of life. Dysphagia and aspiration may cause death in the affected infant. Normal intelligence |
| Treatment | UE management not well documented [26] | Opioid analgesics for severe pain. Supportive treatment of bone crisis bearing in mind increased bleeding risk and abnormal bone [26] | Treat contractures similarly to distal arthrogryposis. Physical and occupational therapy for the hands [26] |
| | *Cornelia de Lange's syndrome* | *Klippel–Trenaunay syndrome* | |
| Description | Syndrome caused by a genetic mutation affecting central nervous system development. Upper extremity involvement consists of a small hand, clinodactyly of the fifth digit, proximally placed thumb, and limited range of motion in the elbow. Radial head dislocation is common. Rarely, ulnar absence and a monodigital hand may occur. Characteristic facial features: corners of mouth are down-turned, synophrys, elongated philtrum, and long eyelashes | Three major features of this developmental disorder—varicose veins, cutaneous capillary-venous malformation, and soft tissue and bone hypertrophy in affected limbs. Overgrowth of bones in girth, length, and width in affected limb. Finger deformities and carpal tunnel syndrome have both been documented | |
| Genetics | Gene—*N1PBL* | | |
| Natural History | Intrauterine growth impedance. Child remains small in size. Low rates of survival in the first year of life. Mental retardation with delayed milstones | Typically presents at birth or infancy | |
| Treatment | Most deformities are asymptomatic limiting the utilization of surgical intervention [26] | Regular compression has shown good results in the hypertrophied limb. Surgery may be utilized only in cases of severe debilitating deformities [26] | |

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