Skeletal Dysplasias

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Abstract

Skeletal dysplasias (SD) are a heterogeneous group of genetic disorders of skeletal growth and development resulting in abnormal shape, size, and texture of skeleton and characterized by short stature. With recent advances in research capabilities in genomics and molecular biology, the genetic basis and molecular mechanisms underlying many of these dysplasias have been elucidated and the classification and nosology have now been expanded to over 400 types. Many of the severe forms of SD do not survive beyond the first week of life. The most common conditions seen in the clinic are achondroplasia and osteogenesis imperfecta, both of which are caused by gene mutations. The diagnosis of SD can often be made prenatally with biometric measurements of the fetus during gestation. After delivery, diagnosis can be made on clinical and radiological features with the aid of biochemical investigations and genetic testing. Upper limb manifestations of SD are also diverse. Commonly seen conditions in the clinic involving upper limbs include osteochondroma (Ollier disease), hereditary multiple exostoses (HME), and fibrous dysplasia. The management of SD requires a multidisciplinary team approach involving a pediatric geneticist, molecular pathologist, radiologist, and pediatric orthopedic surgeon. Genetic counseling plays an important part in the overall management of these disorders. Orthopedic management is mainly directed at treating the manifestations of the disease such as spine and limb deformities and fractures. Current research on treatment by bone marrow transplantation, stem cell therapy, and gene therapy is ongoing.

Introduction

Skeletal dysplasias (SD) are a heterogeneous group of mainly genetic disorders involving disorders of osteochondral development resulting in abnormal shape, size, and texture of the skeleton. Persons with SD can often be recognized by their short stature and disproportion of the head, limbs, and spine. Over 400 types have been described. Birth prevalence of SD recognizable in the neonatal period is 2.4 per 10,000 deliveries (Camera et al. 1982). Twenty-three percent are stillborn and thirty-two percent die during the first week of life. Approximately 9.1 per 1,000 die in perinatal period. Thanatophoric dysplasia and achondrogenesis account for 62 % of all lethal cases. Most common SDs seen in clinical practice are achondroplasia and osteogenesis imperfecta (OI). These four dysplasias represent two-thirds of all the cases of SD.

As the clinical manifestations of SD are quite diverse, one simple way to think about the various types of conditions is to consider that the manifestations can be due to (a) abnormal bone growth (resulting in abnormal shape and size of the skeleton), (b) abnormal number of bones (more or less than normal), and (c) abnormal texture of the bones (increased or decreased bone density).

Classification

The classification of SD was previously based on radiological features, histology, and clinical features. Most were also referred to by their eponyms, by terms describing a salient feature of the disease, or by the presumed pathogenesis of the disease. The fundamental problem encountered previously was that the exact pathogenesis of these diseases was rarely known.

In the 1960s and 1970s, it was recognized that genetic skeletal disorders were clinically and genetically heterogeneous and this prompted a group of international experts from genetics, pediatrics, orthopedics, and radiology to come together to reach a consensus on the nomenclature of what was then recognized as "constitutional (or intrinsic) disorders of bone" (McKusick and Scott 1971). The skeletal disorders were initially grouped into five categories: osteochondrodysplasias, dysostoses, idiopathic osteolyses, chromosomal aberrations, and primary metabolic abnormalities. Numerous revisions were made in the 1970s to early 1990s to address the increasing complexity of information on these skeletal disorders.

In 1999, the International Skeletal Dysplasia Society (ISDS) was formed, and since then, the Nosology and Classification of Genetic Skeletal Disorders have been delegated to an ad hoc group within the ISDS. This nosology provides an overview of recognized diagnostic entities and groups them according to clinical and radiographic features and molecular pathogenesis.

In the 2010 revision of the nosology, 456 conditions were included and placed in 40 groups defined by molecular, biochemical, and/or radiographic criteria (Warman et al. 2011).

The following Table 1 gives an overview of the different groups and their corresponding diagnostic criteria.

Table 1 Overview of the various groups and diagnostic criteria adapted from the Nosology and Classification of Genetic Skeletal Disorders, 2010

Group	Diagnostic criteria
1–8	Based on a common underlying gene or pathway (e.g., achondroplasia belongs to group 1 or the FGFR3 chondrodysplasia group)
9–17	Based on the localization of radiographic changes to specific bone structures (vertebrae, epiphyses, metaphyses, diaphyses, or a combination thereof) or of the involved segment (rhizo, meso, or acro)
18–20	Defined by macroscopic criteria in combination with clinical features (bent bones, slender bones, presence of multiple dislocations)
21–25, 28	Takes into account features of mineralization (increased or reduced bone density, impaired mineralization, stippling, osteolysis) (e.g., osteogenesis imperfecta and other disorders of decreased bone density belong to group 25)
26	Identification of several novel molecular mechanisms leading to hypophosphatemic rickets
27	Lysosomal disorders with skeletal involvement
29	Disorders with so-called abnormal development of skeletal components (exostoses, enchondromas, and ectopic calcification)
30	Overgrowth syndromes with significant skeletal involvement
31	Genetic inflammatory/rheumatoid-like osteoarthropathies
32–40	Dysostoses, anatomical criteria with additional criteria reflecting principles of embryonic development such as limb reduction or hypoplasia (proximal-distal growth) versus terminal differentiation and patterning of the digits or joint formation

Pathogenetics

Recent advances in the understanding of the various causes of SD have been due in large part to the study of the underlying molecular mechanisms and gene mutations (Superti-Furga et al. 2001). SD can be broadly grouped on the basis of the function of the protein product of the causative gene. This can be clinically relevant as many of the disorders caused by genes whose protein products have similar functions also share similar clinical characteristics. Five broad groups can be categorized based on the defective molecular component and proteins/genes involved as shown in Table 2 below.

Many of the genes mutated in SD affect important functions of the growth plate (physis). A good understanding of growth plate physiology will be helpful in working out the possible effects of gene mutations in various zones of the physis. For example, in the resting zone, SOX9 gene mutation causes camptomelic dysplasia; in the proliferative zone, FGFR3 gene mutation causes achondroplasia, hypochondroplasia, and thanatophoric dysplasia; in the hypertrophic zone, PTHR1 gene mutation causes metaphyseal dysplasia; and in the terminal differentiation zone, RUNX2 gene mutation causes cleidocranial dysplasia (Dietz and Mathews 1996; Zelzer and Olsen 2003).

Diagnosis

The diagnosis of SD usually requires a multidisciplinary approach with the active participation of a pediatric geneticist, a radiologist, and a molecular pathologist with special interest in SD as well as a pediatric orthopedic surgeon.

Prenatal Diagnosis

Long-bone biometry has been used extensively in the prediction of the fetal gestational age. Nomograms generally use the long bone as the independent variable and the estimated fetal age as the dependent variable. However, in order to assess the normality of bone dimensions, the gestational age is used as the independent variable and the long bone as the dependent variable. Patients at risk for SD should seek prenatal care early to assess all clinical estimators of gestational age. In the prenatal diagnosis of infants with SD, there is a discrepancy between fetal size and gestational age. Affected fetuses have been shown to have dramatic deviations from the 5th and 95th confidence limits (Romero et al. 1998). The graphs below show the biometry of the femur and humerus during gestation (Figs. 1 and 2).

Table 2 Pathogenetics of SD: 5 broad groups based on the defective molecular component and proteins/genes involved

Gene or protein involved	Clinical phenotype
Group 1: defect in structural cartilage proteins	
Collagen 2 (COL2A1)	Achondrogenesis 2, spondyloepiphyseal dysplasia, Kniest dysplasia, Stickler syndrome
Group 2: defect in cartilage metabolic pathways	
Diastrophic dysplasia sulfate transporter	Diastrophic dysplasia, achondrogenesis IB, atelosteogenesis type 2, recessive multiple epiphyseal dysplasia
Group 3: defect in local regulators of cartilage growth	
Fibroblast growth factor receptor 3 (FGFR3)	Achondroplasia, thanatophoric dysplasia, hypochondroplasia
Group 4: defect in transcription factors	
Short-stature homeobox gene (SHOX)	Dyschondrosteosis, Langer-type mesomelic dysplasia
Group 5: defect in tumor-suppressor genes	
Exostosin 1 and 2	Multiple hereditary exostoses

Postnatal Diagnosis

History

When presented with a child with disproportionate short stature, a focused history can give important clues as to the differential diagnosis. A complete prenatal history should be obtained, including fetal biometry findings during the prenatal ultrasound.

As a part of the patient's perinatal history, it is important to ascertain the patient's birth length, as some patients with skeletal dysplasia may present with short stature at birth (e.g., achondroplasia)

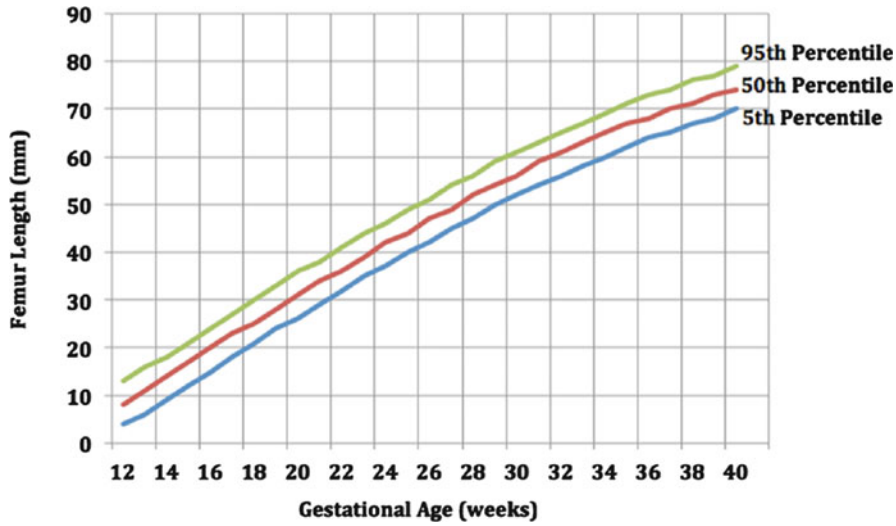

Fig. 1 Biometry of femur during gestation

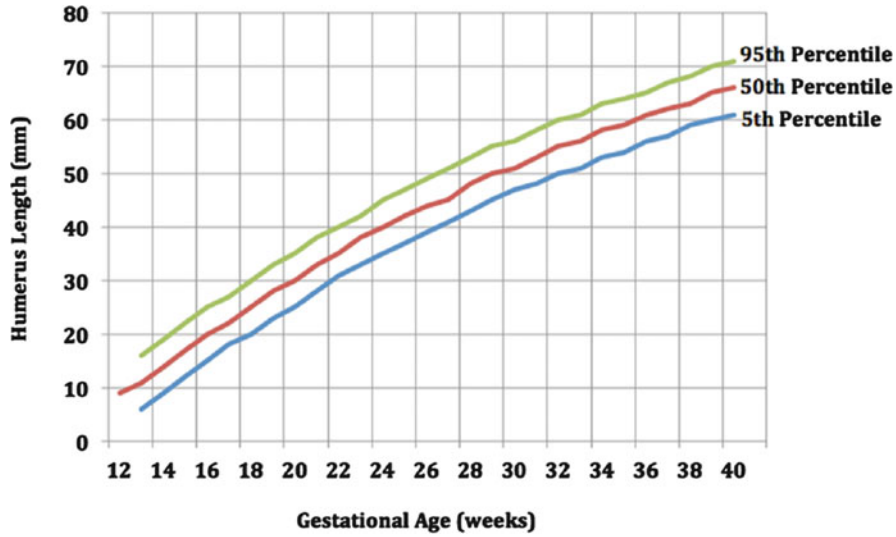

Fig. 2 Biometry of humerus during gestation

while others may have a normal birth length with subsequent failure of linear growth (e.g., pseudoachondroplasia).

Family Evaluation

It is important to take a detailed family history to determine if there is another family member with SD in order to assess the mode of inheritance, if any. SD is often transmitted by Mendelian inheritance. A pedigree that includes first-degree relatives is usually sufficient for screening, but occasionally, a more extensive family history is needed. Assessment of parental heights also plays a role, as the child simply might have familial short stature (Unger 2002).

Physical Examination

Growth parameters should be measured, which include the patient's height, weight, and head circumference. For example, in patients with achondroplasia, the head circumference is greater than normal while the height is reduced dramatically. It is also important to note the height for age percentile of the patient. In general, if adult height is under 150 cm or 5 ft, consideration of SD is appropriate.

It is also necessary to determine the patient's proportions. The upper segment to lower segment ratio and the arm span to height ratio are used to document whether the spine or the limb is more severely shortened. Limb shortening is further classified depending on which segment is most affected: rhizomelia (short proximal segments; i.e., short humerus or femur, as in achondroplasia), mesomelia (short middle segments; i.e., short forearm or tibia, as in dyschondrosteosis), or acromelia (short hands or feet, as in Grebe type of chondrodystrophy) (Fig. 3).

When the patient is short but the body proportions are normal, the diagnosis is usually related to constitutional short stature, which may be due to endocrine disorders, malnutrition, prenatal dwarfism, or one of the many dysmorphic syndromes.

Patients with SD often have dysmorphism or minor morphologic variations of the bones and soft tissues. Dysmorphic features associated with short stature suggest an underlying SD (Beals and Horton 1995).

The presence of deformities (e.g., spinal deformities such as lordosis, kyphosis, or scoliosis; varus or valgus deformity of the extremities) in patients with short stature is also highly suggestive of a diagnosis of an SD.

Imaging Studies

Good-quality skeletal radiographs should be obtained. It is necessary to request for a limited

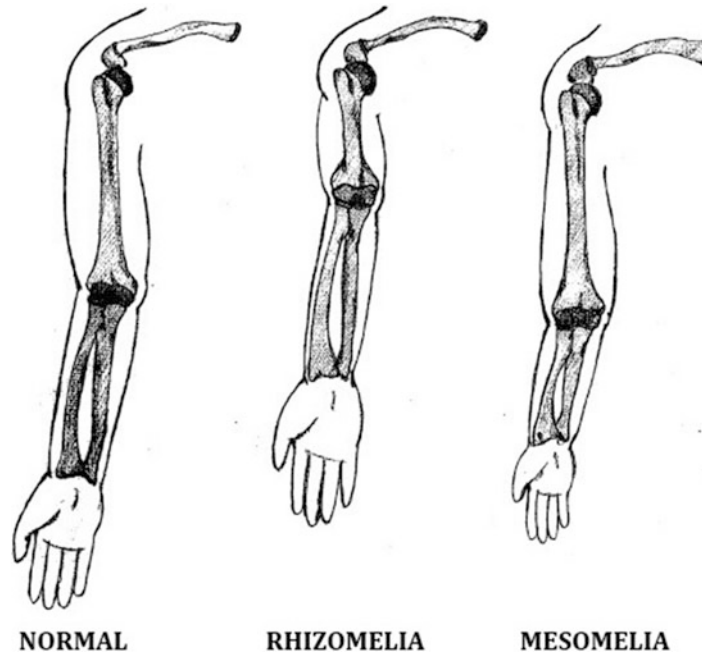

Fig. 3 Types of disproportionate limb shortening

skeletal survey because normal findings in a specific region can aid in making a differential diagnosis. An SD can almost always be diagnosed on the basis of five radiographs: lateral skull, anteroposterior (AP) view of the pelvis, lateral lumbar spine, AP view of the hand and wrist, and AP view of the knee. In general, the dysplasias are classified according to which part of the skeleton is involved. The pattern of involvement may include any or all of the following: spondyloepiphyseal, metaphyseal, and diaphyseal dysplasia. Aside from the pattern of involvement, the region affected can also be used to narrow the differential diagnosis (Unger 2002).

Other Tests

Many of the SD can be diagnosed from clinical and radiographic features. However, a blood chemistry profile can be obtained to exclude treatable metabolic disorders such as the mucopolysaccharidoses and rickets. A bone biopsy is rarely indicated but may sometimes be useful to confirm the diagnosis of dysplasia. In some instances, more detailed genetic testing may be required for purposes of confirmation of the diagnosis, documentation, and counseling.

Differential Diagnosis

In considering the differential diagnosis, a few important conditions should come to mind. These are hypothyroidism, nutritional rickets, failure to thrive, and non-accidental injuries.

General Approach to Treatment

A multidisciplinary approach is usually required to manage SD as the children often have multiple problems that require different areas of expertise. Genetic counseling is an important aspect of management and a pediatric geneticist would be the ideal person to conduct this appraisal. In centers where antenatal diagnostic technology is available, preimplantation genetic diagnosis could help the parents to have a normal child. In addition to genetic counseling, the parents and child will benefit from counseling with respect to potential medical and social problems that the child could encounter during growth and development.

More specific to the type of SD, the child will require management for spine and limb

deformities, possible fractures (e.g., in osteogenesis imperfecta), limb length discrepancy, and in some situations limb lengthening for short stature. Some of these will be covered in greater detail in the sections below on Achondroplasia and Osteogenesis Imperfecta.

Commonly Seen Conditions

Achondroplasia

Achondroplasia is the most common SD, with an incidence of 1 in 30,000 live births per year (Shirley and Ain 2009). It is inherited as a fully penetrant autosomal dominant trait. However, more than 80 % of the cases are sporadic, wherein affected individuals are the offspring of parents of normal stature. Higher paternal age at the time of conception of patients with achondroplasia suggests that de novo mutations of paternal origin are involved (Vajo et al. 2000).

Pathogenetics

Achondroplasia is caused by mutations of the gene encoding fibroblast growth factor receptor 3 (FGFR3) on the distal short arm of chromosome 4. Most individuals with the clinical features of achondroplasia have the same mutations that substitute an arginine for a glycine residue in the transmembrane domain of the receptor in the physis. FGFR3 is a negative regulator of chondrocyte proliferation and differentiation in the growth plate. Mutations involving the FGFR3 result in activation of the receptor and thus viewed as a gain-of-function mutation (Vajo et al. 2000; Horton 2006; Laederich and Horton 2010).

The clinical result of this mutation is underdevelopment and shortening of the long bones formed by endochondral ossification. It has been suggested that FGFR3 inhibits both the proliferation and terminal differentiation of growth plate chondrocytes and synthesis of extracellular matrix by these cells. It also proposed that FGFR3 induces premature terminal differentiation, thereby reducing the number of cells that contribute to template synthesis (Laederich and Horton 2010).

Prognosis

Affected individuals have normal cognitive development, although motor development may be delayed. Patients with achondroplasia are healthy compared to patients with other skeletal dysplasias, but mortality rates in all age groups are higher than those in the general population because of sudden death in young infants, central nervous system and respiratory problems in older children, and cardiovascular problems in young adults.

Diagnosis

The clinical manifestations of achondroplasia vary at different stages of the affected individual's life.

At birth, short stature is evident, with the trunk length in the lower range of normal and the extremities shortened in a rhizomelic pattern. Frontal bossing and midface hypoplasia are also noted. Delayed motor development or apnea in infants may be the result of foramen magnum stenosis leading to cervical myelopathy. Hydrocephalus may occur during the newborn and infantile period.

As the infant grows and begins to sit, thoracolumbar kyphosis may be noted. This is often due to the infant slumping forward because of trunk hypotonia combined with a relatively oversized head, a flat chest, and a protuberant abdomen. This decreases with age (most tend to resolve at 12–18 months of age) as trunk strength improves and the child begins to walk.

As the child continues to grow, genu varum and lumbosacral hyperlordosis become evident. The presence of genu varum is a clinical hallmark of achondroplasia. Its cause remains controversial, with several hypotheses being proposed such as lateral collateral ligament laxity and fibular overgrowth. Lumbosacral hyperlordosis is the result of excessive anterior pelvic tilt while standing, producing a prominent abdomen and buttocks with hip flexion contractures. In adulthood, lumbar spinal stenosis may develop.

The rhizomelic shortening of the upper extremity of affected individuals can create disability because of the difficulty in reaching the top of the head and the perineum for hygiene care.

This can also be exacerbated by elbow flexion contractures and radial head subluxation.

The average final height of adult individuals with achondroplasia is 132 cm for males (range: 118–145 cm) and 125 cm for females (range: 112–136 cm). This corresponds to a height that is 6–7 standard deviations below the average for unaffected individuals (Shirley and Ain 2009).

Management

Management of achondroplasia is directed toward its different clinical manifestations. Indications for surgery for the spinal conditions associated with achondroplasia are not clearly defined, although neurologic compromise generally warrants appropriate surgical intervention. The decision for limb lengthening is likewise difficult and controversial, as the lengthening process is long, arduous, and complicated. In addition, the functional improvement after elective limb lengthening has not been well established.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is a heritable heterogeneous disorder of bone formation that may affect more than 1 in 10,000 individuals. It is distinguished by four features that present in the following causal relationship: genetic disorder, collagen defect, bone fragility, and frequent fracture. Patients with OI are characterized by having fragile bones. Many also have dentinogenesis imperfecta (teeth appear brownish or bluish, soft, translucent, prone to cavities, and crack easily), blue sclerae (the effect of light reflected from the underlying choroid and its blood vessels through the thin sclerae), and scoliosis (Roughley et al. 2003). Minimal trauma can result in fractures and bony deformities.

Pathogenetics

OI is a group of disorders caused by inherited or spontaneous genetic mutations in the COL1A1 or COL1A2 genes, which are responsible for encoding the alpha-1 and alpha-2 chains of type 1 collagen, respectively. Quantitatively or qualitatively deficient fibrils are produced by mutations in these genes, resulting in bone tissue with altered mechanical properties. Bone tissue anomalies are the most visible manifestation of OI. Extraskeletal tissues and organs affected by type 1 collagen defects include the sclerae, dentine, ear ossicles, skin, vessels, capillaries, and heart valves.

Classification

In 1979, Sillence classified the condition into four types based on clinical, genetic, and radiographic findings. Since then, three more types have been added. Types I to IV are commonly associated with mutations in the genes for type 1 collagen, whereas no type 1 collagen gene mutation has been detected in types V to VII (Kocher and Shapiro 1998; Burnei et al. 2008).

Type I

Type I is the most common form of OI, estimated at 3–5 per 100,000 births. It is mild in severity and is inherited in an autosomal dominant pattern. Patients have blue sclerae and bone fragility and are deaf or have a family history of presenile deafness. Infants are of normal weight and length at birth and do not have multiple fractures. This type is subdivided into type A and type B according to the absence or presence of dentinogenesis imperfecta, respectively.

Type II

This is the lethal form of OI, and the pattern of inheritance is also autosomal dominant. However, the lack of affected siblings in different series suggests a new mutation of a dominant gene or a nongenetic etiology. Its incidence is 1 per 40,000–60,000 births. Infants are either stillborn or die during the neonatal period and are frequently small for gestational age. Blue sclerae are present. In utero, multiple fractures occur and the long bones are broad and shortened.

Type III

This is the most severe nonlethal form of OI, and the pattern of inheritance for this type is autosomal dominant. Its incidence is 1–2 per 100,000

births. During infancy, patients have bluish sclerae. Later in life, they have normal or pale blue sclerae. In most patients, the long bones are shortened and bowed, and multiple fractures are present at birth. This type is characterized by progressive deformity of the long bones and spine. Dentinogenesis imperfecta is also present.

Type IV

This type is rare, with an unknown frequency. It is the clinically most diverse group and is inherited as an autosomal dominant disorder. It encompasses all those individuals who do not meet the criteria for types I to III. The phenotype can vary from mild to severe, and the more severely affected patients present with fractures at birth and have moderate skeletal deformity and a relatively short stature. Affected individuals have blue sclerae at birth that eventually become white. The long bones are of normal length, but there may be mild femoral bowing noted. It is subdivided into type A and type B according to the absence or presence of dentinogenesis imperfecta, respectively.

Type V

Type V OI is moderately deforming, and patients exhibit moderate to severe bone fragility. It is inherited in an autosomal dominant manner and is characterized by hypertrophic callus development after fracture, calcification of the interosseous membrane at the forearm, and hyperdense metaphyseal bands. Blue sclerae and dentinogenesis imperfecta are absent.

Type VI

This type of OI presents with moderate to severe skeletal deformity. It is characterized by frequent fracture, vertebral compression, long-bone deformity, normal-colored sclerae, and the absence of dentinogenesis imperfecta. Blood tests show slightly elevated levels of serum alkaline phosphatase. Histologic studies show fish-scale-like appearance of the bone lamellae and an abundance of osteoid, unmineralized bone matrix in the absence of hypocalcemia or abnormalities in phosphate, parathyroid hormone, or vitamin D metabolism.

Type VII

Patients with this type of OI also have moderate to severe skeletal deformity and bone fragility. Unlike other forms of OI, which are autosomal dominant in transmission, type VII OI is autosomal recessive in inheritance. The distinctive features of this type are rhizomelic limb shortening and coxa vara. Affected individuals lack blue sclerae and dentinogenesis imperfecta.

A summary of the Sillence classification is shown in Table 3 below.

Prognosis

Osteogenesis imperfecta is a disease with a wide range of clinical presentations; thus, the quality of life of patients with OI is highly variable. Type II OI is lethal. Type I OI has the best prognosis as the presence of multiple fractures is uncommon. Types III to VII OI, although compatible with life, can lead to significant handicaps due to multiple fractures and deformities.

Diagnosis

Prenatal diagnosis of OI can be made with ultrasound. Type II OI has been diagnosed before 20 weeks age of gestation, with findings of long-bone fractures, angulation, shortening, localized thickening secondary to callus formation, bowing, and demineralization (Fig. 4). Multiple fractures are also noted in the ribs resulting in a narrowed chest. The skull may be thinner and, in severe cases, the cranial vault has a wavy outline and is easily compressible.

Although prenatal ultrasound can accurately diagnose type II OI, it has been unsuccessful in diagnosing the other types of OI, as there are limitations to the evaluation of bone mineralization with sonography.

At birth, the Sillence classification helps to establish the diagnosis, but only when the clinical signs are obvious. The presence of blue sclerae and a positive family history are the most reliable features.

Biochemical and genetic examinations based on the study of type 1 collagen and DNA may be necessary to differentiate OI from non-accidental injury (NAI). These examinations are also useful

Table 3 Sillence classification with additional types more recently described

Type	Severity	Inheritance	Features
I	Mild	Autosomal dominant	Blue sclerae; bone fragility; infants are of normal weight and length at birth without multiple fractures
			Type A: normal teeth
			Type B: dentinogenesis imperfecta
II	Lethal perinatal	Autosomal dominant	Blue sclerae, stillborn or neonatal death, multiple intrauterine fractures
III	Severe deforming	Autosomal dominant	Normal or pale blue sclerae, multiple fractures present at birth, progressive deformity of long bones and spine, dentinogenesis imperfecta
IV	Mild to severe	Autosomal dominant	Normal sclerae, moderate skeletal deformity, relatively short stature
			Type A: normal teeth
			Type B: dentinogenesis imperfecta
V	Moderately deforming	Autosomal dominant	Normal sclerae, moderate to severe bone fragility, hypertrophic callus development after fracture, calcification of the interosseous membrane at the forearm, hyperdense metaphyseal bands, normal teeth
VI	Moderate to severely deforming	Autosomal dominant	Normal sclerae, frequent fracture, long-bone deformity, normal teeth, fish-scale-like appearance of bone lamellae, and an abundance of osteoid unmineralized bone matrix
VII	Moderate to severely deforming	Autosomal recessive	Normal sclerae, normal teeth, rhizomelic limb shortening, coxa vara

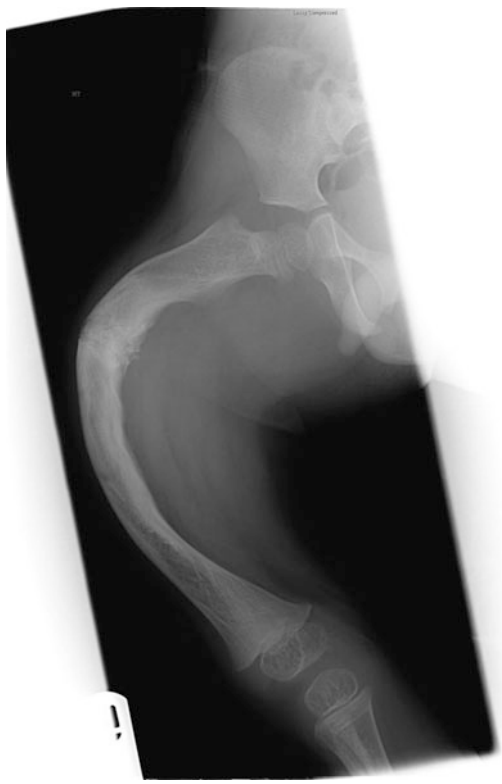

Fig. 4 Bowed femur in a 12-year-old boy with osteogenesis imperfecta

to distinguish OI from other genetic syndromes such as hypophosphatasia and vitamin D disorders that are associated with frequent fractures but exhibit no structural alteration of type 1 collagen.

Bone mineral density (BMD) measurement can also be used in the diagnosis of OI. Although measured values can be normal in a small number of cases, most patients with OI have BMD values far below the normal range, which can be a major risk factor for further fractures.

Management

The goals of treatment in children with OI include reduction of fracture rates, correction and prevention of long-bone deformities and scoliosis, and improvement of functional outcome.

The use of bisphosphonates in children with OI, whether in oral (alendronate) or intravenous (pamidronate) form, has been shown to demonstrate a decrease in the frequency of fractures as well as improvement of vertebral bone density and quality of life (Rauch et al. 2003; DiMeglio and Peacock 2006). The duration of treatment must be limited to approximately 2 years, as bone mineral density tends to stabilize or even

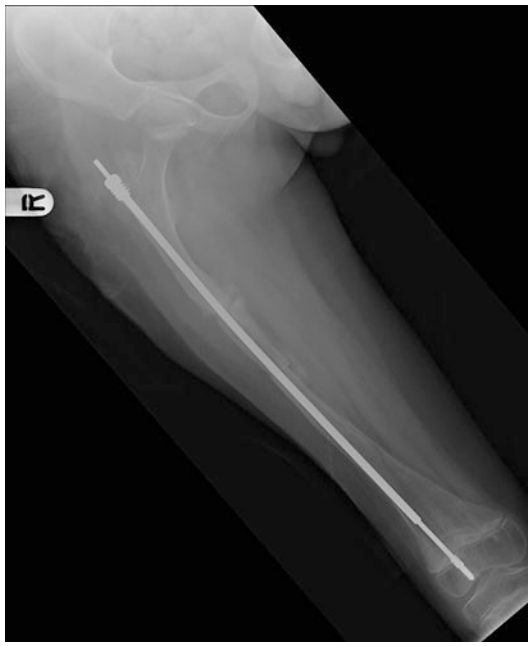

Fig. 5 Osteotomy of femur and insertion of Fassier-Duval (FD) telescoping nail

decrease after the first 2 years of treatment. It is also important to note that bisphosphonates interfere with bone formation and resorption; hence, interference with healing following a fracture or osteotomy is expected (Munns et al. 2004). Often, the bisphosphonates are discontinued for short duration before and after a planned osteotomy.

Surgical management in patients with OI includes treatment of fractures as well as correction of long-bone and spinal deformities, followed by early physical therapy in order to restore the patient to self-sufficiency as completely and rapidly as possible. Internal fixation of long bones using intramedullary rods or nails is the most common surgical treatment for patients with OI. Multilevel long-bone osteotomies as originally described by Sofield (Sofield and Millar 1959) in combination with the use of intramedullary devices, whether telescopic or non-telescopic, have been beneficial in the restoration of the bony axis in patients with OI (Fig. 5). In order to address scoliosis in patients with OI, Luque instrumentation (Hanscom et al. 1992) is a reliable option in these patients. Although bone fragility may be a deterrent to spinal instrumentation, the use of bisphosphonates generally improves the quality of bone, thereby allowing the use of instrumentation (Burnei et al. 2008).

Current research is directed toward the implantation of smart intramedullary rods and bone marrow transplantations as viable treatment options for patients with OI.

Upper Extremity Manifestations of SD

The spectrum of conditions under this diagnostic umbrella is wide, so the upper limb manifestations in skeletal are predictably diverse and heterogeneous. This situation has been accentuated with the increased number of "skeletal dystoses" included in the latest revision of the classification of these disorders by the International Skeletal Dysplasia Society in 2010 (Warman et al. 2011).

The etiology of the upper limb problems is varied and may be multifactorial. The clinical problems encountered may be attributed to mass effect, growth disturbances, propensity to injury, poor healing capacity, and in some cases malignant change.

Certain deformities are more commonly associated with particular diagnoses. This section will focus on the range of upper limb problems in patients with SD, and these will be discussed in the context of the types of underlying conditions that they are usually associated with.

Clinical Presentation and Management

The diagnosis of SD may be made prenatally, but more often than not, it may only be obvious at birth or even later. In some cases, the problem in the upper limb may be the main reason for the child to consult a physician. While SDs are uncommon, with an incidence of about 1 in 5,000 live births (Alanay and Lachman 2011), it is important to consider the possibility of this diagnosis when a patient presents with features of SD or a problem consistent with it.

As discussed above, the clinical evaluation should include an assessment of height and limb lengths (including proportions of segments).

A radiological assessment of the affected limb is necessary, and that of the contralateral limb is often helpful to provide a basis for comparison. Depending on the condition, the patient may have generalized laxity (e.g., Marfan's syndrome, hypochondroplasia) or contractures (e.g., camptodactyly with SD).

Short Upper Limb and Limb Length Discrepancy

A short upper limb is part of the presentation of the short stature in SD. Depending on the type of short stature, the limb may be rhizomelic, mesomelic, or acromelic. Limb shortening is seen not just in disorders like achondroplasia but also conditions like Ollier disease and hereditary multiple exostoses (HME). The growth effects of Ollier disease are more severe than in HME, leading to a shortened and enlarged bone.

However, bony involvement extends beyond shortening. There is also associated bone bending and curvature. This increases the effective shortening and can limit motion, thus limiting the available working space of the limb. The affected regions are also associated with increased risk of fractures. Limb involvement may be asymmetric, for example, in Ollier disease and HME, leading to limb length discrepancy. Apart from appearance, limb length discrepancy is better tolerated in the upper limb compared to the lower limb.

Joint or Bony Deformity

Shoulder Deformities

Kosenow syndrome, or pelvis-shoulder dysplasia, is a rare SD that has its main features as bilateral iliac and scapular hypoplasia (Elliott et al. 2000).

Arm and Elbow Deformities

Achondroplasia is often associated with a short humerus, posterior bowing of the elbow, and a subluxation of the radial heads. The elbow deformity results in loss of elbow extension (Kitoh et al. 2002). The radial head dislocation can cause a secondary compressive injury to the posterior interosseous nerve.

Forearm Deformities

In HME, deformities of the forearms are common. Typically, it appears like a Madelung deformity, leading to forearm shortening and bowing giving the appearance of a varus deformity of the forearm and elbow (see chapter ▶ "Benign Bone Lesions"). Forearm pronation and supination are also restricted. Lengthening of the ulna can correct the deformity to a large extent. Hypoplastic or absent radii is seen in Fanconi anemia.

Hands

The manifestations in the hand are varied. Achondroplasia patients have "trident hands," i.e., an extra space between the 3rd and 4th ray, so that the fingers are divided into 3 groups. Deformities include polydactyly, ectrodactyly, brachydactyly, camptodactyly, synostosis, thumb hypoplasia (e.g., Holt-Oram syndrome, Fanconi anemia), and syndactyly (e.g., Apert syndrome). A short metacarpal is a frequent manifestation in HME (Pannier and Legeai-Mallet 2008).

In Fanconi anemia, the hand deformity may be first presentation of the clinical problem (Kozin 2008). Especially where there are additional findings such as growth retardation, skin hyperpigmentation, and microcephaly, this diagnosis should be considered and further evaluation done.

Pain

Localized pain may be due to stress fractures, mechanical effects of swellings on surrounding structures, or rarely malignant change. It has been reported that female patients with fibrous dysplasia can have increased pain during pregnancy and during parts of the menstrual cycle because of the effect of estrogen on the lesions (Kaplan et al. 1988).

Fractures and Bony Deformity

Patients with SD may have propensity to fractures due to localized (e.g., Ollier disease) or generalized deficiencies in the mechanical properties of the bone (e.g., osteogenesis imperfecta). On occasion, the development of a fracture due to a trivial injury may be the trigger to the diagnosis of the underlying condition. Besides the usual morbidity

associated with fractures, there is an increased likelihood of development of deformity due to poor bone remodeling in these patients.

In osteogenesis imperfecta (OI), fractures of the shoulder and upper extremity were found to be common in an inpatient cohort of OI patients, with 66 % of them having such an injury (Sułko 2004). These patients have a 33–37 % incidence of upper extremity deformities, with the humerus, radius, and ulna being the most commonly affected bones. Beyond appearance, upper limb deformities can affect functional activities and interfere with activities of daily living.

While most cases of fractures in OI occur in known patients with the diagnosis, a fracture may be the initial presentation for the condition. Zionts and Moon reported a series of patients with OI who sustained fractures of the apophysis of the olecranon, mostly after trivial trauma. The fractures occurred at a mean age of 10, and half of the patients were not known to have OI at the time of elbow fracture (Zionts and Moon 2002).

Enchondromatosis (Ollier disease) affects the short tubular bones of the hand and feet, as well as the extremity long bones. It is not uncommon for enchondromas to be diagnosed as incidental findings when an X-ray is done for some other reason. Enchondromas give rise to focal areas of weakness of tubular bones leading to pathological fractures. When there is a fracture, it is necessary to treat both the fracture and the underlying enchondroma. The standard treatment for the lesion is curettage, bone grafting, osteotomies, and internal fixation. In a case report, it has been suggested that distraction osteogenesis can be used to treat the deformity as well as the shortening following a humeral fracture, as well as conversion of the diseased to normal bone (Tellisi et al. 2008).

Fibrous dysplasia is a benign intramedullary fibro-osseous lesion. It most commonly affects a single bone (monostotic) but can affect multiple bones (polyostotic form). McCune-Albright syndrome is a rare disease that presents with polyostotic fibrous dysplasia associated with café au lait spots and endocrinopathy. The monostotic form may be asymptomatic and is often diagnosed incidentally, but it can present with pain, deformity, and pathological fractures. The risk of fracture is high in polyostotic fibrous dysplasia. In a cohort study of 35 patients, 172 fractures were reported at mean follow-up 14.2 years. Of these, 44 of them involved the humerus and forearm bones (Leet et al. 2004). Figure 6 shows radiographs of fibrous dysplasia involving the humerus, radius, and ulna with the typical ground-glass appearance.

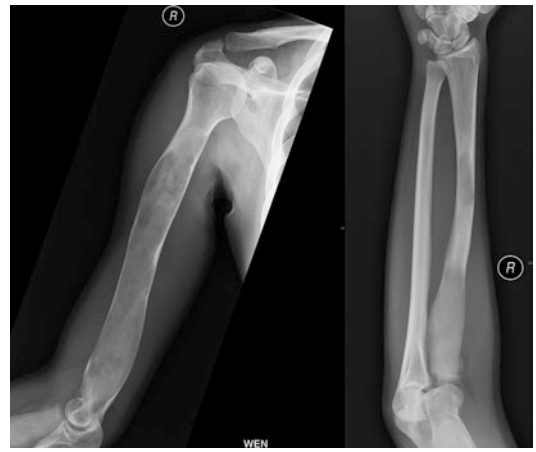

Fig. 6 Polyostotic fibrous dysplasia showing lesions in the humerus and radius

Nerve Problems

Involvement of the central nervous system is a well-recognized problem in SD. However, the peripheral nervous system can also be affected from the manifestations of the disease. The peripheral nerve can be affected by traction, compression, or injury at the level of the nerve roots or nerve itself. Multiple factors can cause nerve injury including compression or traction due to bony deformity or swellings. In achondroplasia, the posterior interosseous nerve may be injured with a radial head subluxation or dislocation. There are also risks and the possibility of iatrogenic injury during surgery. For example, patients with SD are more likely to sustain nerve injury during limb lengthening procedures (Nogueira et al. 2003).

The development of carpal tunnel syndrome (CTS) in children is associated with mucopolysaccharidosis (MPS). MPS is the most common

cause of CTS in children. The condition is caused by deposition of glycosaminoglycans (GAGs) in the flexor retinaculum and tenosynovium, causing compression of the median nerve. It should be noted that CTS presents differently in children. The typical sensory symptoms are usually absent and most patients deny any symptoms (Haddad et al. 1997). The main presenting complaint is difficulty with fine motor activities or manual clumsiness, which may be first noticed by the caregiver. Examination findings are also different, with unreliable Phalen's and Tinel's signs. Early surgical treatment gives better results, so a high index of suspicion is necessary and early nerve conduction studies are useful. The treatment of choice is surgical release of the carpal tunnel with concomitant flexor tenosynovectomy and A1 pulley release.

Other Upper Limb Problems

Children with MPS are prone to the development of trigger digits. The underlying pathology is similar to that of carpal tunnel syndrome in these patients, with deposition of GAGs around the flexor tendon at the level of the A1 pulley. If untreated, the condition can lead to flexion contracture of the digits. The recommended treatment is release of the trigger with a possible need to partially resect the flexor digitorum superficialis tendon (Van Heest et al. 1998). The surgery is often done concurrently with the release of the carpal tunnel (White and Sousa 2013).

Malignant Change

Malignant change is an uncommon but serious problem associated with some conditions. Enchondromatosis (Ollier disease and Maffucci syndrome) is associated with malignant change of the enchondroma to chondrosarcoma. The estimated risk varies between 20 % and 50 %. Maffucci syndrome has been shown to be associated with a high risk of malignant change, and also with poorer prognosis (Pannier and Legeai-Mallet 2008).

In hereditary multiple exostoses, there is an associated risk of malignant transformation of the osteochondroma (Pannier and Legeai-Mallet 2008). Malignant change is more likely to involve the axial bones, such as the pelvis, scapula, ribs, and spine. Malignant change is rarely seen in childhood and is more often seen after the end of growth. In patients with enchondromatosis and HME, regular surveillance of the lesions is recommended and it has to be carried out well into adulthood.

Summary and Future Directions

SDs are a heterogeneous group of mainly genetic disorders involving osteochondral development resulting in abnormal shape, size, and texture of bone and short stature. In the recent Nosology and Classification of Genetic Skeletal Disorders (2010), 40 groups have been identified based on molecular, genetic, and radiological criteria. The diagnosis and management of SD are best accomplished by a multidisciplinary team consisting of a pediatric geneticist, a molecular pathologist, a radiologist, and a pediatric orthopedic surgeon. Genetic counseling forms an important part of the management. Many of the clinical manifestations of SD will require the expertise of a pediatric orthopedic surgeon with special interest in deformity correction and limb reconstruction.

Current genetic approaches in research on achondroplasia have been directed at interfering with the synthesis of the FGFR3 gene, or blocking its activation, or inhibiting its tyrosine kinase activity, or promoting its degradation, or antagonizing its downstream signals. Recent studies in transgenic mice with high concentrations of brain natriuretic peptide (BNP) showed increased physeal activity resulting in increased bone growth (Nakao-Lab, Kyoto). A C-type natriuretic peptide (CNP) has been found to antagonize the effects of FGFR3 on endochondral ossification through the MAPK-mediated FGFR3 signals. Rescue of bone growth deficiency was seen in the achondroplastic mice even at a 10-fold lower dose of CNP (Yasoda et al. 2009). Work is currently directed at bringing this to clinical trials.

For osteogenesis imperfecta, there have been some efforts made in using bone marrow transplantation as a way to increase the normal osteoblasts in a child with OI. Horowitz et al. (2001)

reported on 3 children who underwent bone marrow transplantation and showed increased osteoblast density, increased mineralization, and decreased incidence of fractures. These children apparently also grew in height. There are also some efforts directed at using gene therapy to try to convert the more severe types of OI to milder forms. Gene therapy is quite challenging as there is a high mutation spectrum in OI (Marini et al. 2010).

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