Published in final edited form as:
Am J Med Genet A. 2009 June ; 149A(6): 1334–1345. doi:10.1002/ajmg.a.32253.

The Erlenmeyer Flask Bone Deformity in the Skeletal Dysplasias

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Abstract

Erlenmeyer flask bone deformity (EFD) is a long-standing term used to describe a specific abnormality of the distal femora. The deformity consists of lack of modeling of the di-metaphysis with abnormal cortical thinning and lack of the concave di-metaphyseal curve resulting in an Erlenmeyer flask-like appearance. Utilizing a literature review and cohort study of 12 disorders we found 20 distinct disorders were associated with EFD. We interrogated the International Skeletal Dysplasia Registry (ISDR) radiographic database (1988–2007) to determine which skeletal dysplasias or syndromes were highly associated with EFD, whether it was a uniform finding in these disorders, and if forms of EFD could be differentiated. EFD was classified into three groups. The first catogory was the typical EFD shaped bone (EFD-T) resultant from absent normal di-metaphyseal modeling with relatively normal appearing radiographic trabecular bone. EFD-T was identified in: frontometaphyseal dysplasia, craniometaphyseal dysplasia, craniodiaphyseal dysplasia, diaphyseal dysplasia-Engelmann type, metaphyseal dysplasia-Pyle type, Melnick–Needles osteodysplasty, and otopalatodigital syndrome type I. The second group was the atypical type (EFD-A) due to absence of normal di-metaphyseal modeling with abnormal radiographic appearance of trabecular bone and was seen in dysosteosclerosis and osteopetrosis. The third group was EFD-marrow expansion type (EFD-ME) in which bone marrow hyperplasia or infiltration leads to abnormal modeling (e.g., Gaucher disease). Further, radiographic review determined that it was not always a consistent finding and that there was variability in both appearance and location within the skeleton. This analysis and classification aided in differentiating disorders with the finding of EFD.

Keywords

Erlenmeyer flask deformity; skeletal dysplasias; osteochondrodysplasias

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INTRODUCTION

The term Erlenmeyer flask is derived from a type of laboratory flask which has a conical base and a cylindrical narrow neck joined by uncurved edges and was named after the German chemist Richard Erlenmeyer, who created it in 1861. The term, Erlenmeyer flask bone deformity (EFD), has been commonly used to describe an abnormality in the distal aspect of the femora. However, similar deformities had been observed in other long bones including the proximal ends of the humeri and tibiae, and the distal ends of ulnae and radii. The deformity can occur bilaterally or unilaterally. This deformity results from defective bone modeling (under-modeling) at the meta-diaphyseal [di-metaphyseal] region leading to straight uncurved [or even laterally bowed] di-metaphyseal borders and cortical thinning giving the appearance of EFD [Castriota-Scanderbeg and Dallapiccola, 2005]. EFD was first described in a radiograph from the left lower limb of a Nubian mummy [Smith nd Jones, 1910], but without any clear diagnosis. Later in 1967, EFD of distal femora and proximal tibiae was observed in an ancient skeleton from the Mochica culture of Peru. The authors suggested that this represented a case of metaphyseal dysplasia-Pyle type [Urteaga and Moseley, 1967].

Review of the literature showed that EFD has been reported in at least 20 distinct disorders and differentiating these disorders can be challenging because while the finding can be readily visualized, it occurs in relatively rare skeletal disorders and syndromes. Erlenmayer flask has been reported in a heterogeneous group of craniotubular bone dysplasias including frontometaphyseal dysplasia, metaphyseal dysplasia-Pyle type, cranio-meta-diaphyseal dysplasia, diaphyseal dysplasia-Engelmann type, Melnick–Needles osteodysplasty, dysosteosclerosis, and osteopetrosis. Other disorders with EFD similar to Pyle disease have been described, including hypertrichotic osteochondrodysplasia (Cantu syndrome), metaphyseal dysplasia, Braun–Tinschert type, and multicentric fibromatosis with metaphyseal dysplasia [Lachman, 2007]. EFD is commonly seen in other systemic disorders including Gaucher disease, Niemann-Pick disease, thalassemia, and has been reported as a late change in lead poisoning [Beighton and Cremin, 1980; Lachman, 2007].

To determine which skeletal dysplasias or syndromes were highly associated with EFD, whether it was a uniform finding in these disorders, and if types of EFD could be differentiated, we interrogated the International Skeletal Dysplasia Registry (ISDR) radiographic database (1988–2007). Analysis of the cases with this radiographic finding identified a cohort of patients with 12 distinct disorders. Furthermore, three types of EFD were identified, EFD-typical (EFD-T), EFD-atypical (EFD-A), and EFD-marrow expansion (EFD-ME). Classifying our cohort into categories aided in differentiating disorders with the finding of EFD and should aid in the differential diagnosis of a patient with the radiographic finding of EFD.

MATERIALS AND METHODS

The International Skeletal Dysplasia Registry (ISDR) was established in 1968 and is a referral center for the skeletal dysplasias [syndromes] and dysostoses. Over 15,000 referrals have been made to this registry. Each case is analyzed for abnormal radiographic findings in the appendicular and axial skeletal and all abnormalities are categorized and the data placed within a searchable database. In this retrospective study, we analyzed the computerized radiographic data from 1988 to March 2007. The database was queried with the keyword “Erlenmeyer flask deformity” to obtain the list of registered cases for which this finding was noted during radiographic analysis. A total of 50 cases were identified by this retrospective search (Table III).

Each case identified was reviewed to determine the precise diagnosis based on the constellation of abnormal radiographic and clinical findings. Cases with the deformity were analyzed to determine if EFD could be subclassified. EFD-typical (EFD-T) was defined by failure of bone modeling due to several underlying mechanisms that influence the final look of the tubular bone. EFD-T type showed an abrupt transition above the meta-diaphyseal region and lack of di-metaphyseal modeling, in addition to cortical thinning and normal or slightly coarse appearing trabecular bone radiographically (Fig. 2). EFD-atypical (EFD-A) had the same modeling defect as typical EFD, however, the metaphyseal bone trabeculae appeared radiologically abnormal. The last group was EFD-ME in which the bone marrow is expanded as a result of infiltration with abnormal storage material. After it was determined which diagnostic entities or disorders had EFD, the type was determined, and all cases within that diagnostic category [1988–2007] were reviewed to determine whether it was a uniform finding in the disorder and whether bones beyond the distal femora were involved.

RESULTS

The cohort study of the ISDR identified 12 distinct disorders with EFD and review of the literature identified six other disorders bringing the total number of disorders with EFD to 20. The clinical and radiographic findings for all these disorders are represented in Table I and Table II. The disorders then were categorized into three main groups: cranio-tubular bone dysplasias (16 skeletal dysplasias), metabolic disorders and syndromes (3 disorders), and one entity that did not fall into a specific classification.

Initially, there were 61 cases with EFD in the ISDR available for review, however 11 cases were excluded based on indequate information. After review of the 50 available cases, we noted that the appearance of the Erlenmayer flask deformity was not uniform between the disorders. In some disorders there was a characteristic Erlenmeyer flask appearance (EFD-T) (Fig. 1 and Fig. 2). The best examples of this type were seen in Pyle disease, frontometaphyseal dysplasia, craniometaphyseal dysplasia, craniodiaphyseal dysplasia-dominant type, cranio-meta-diaphyseal dysplasia-wormian bone type, Camurati–Engelmann diaphyseal dysplasia, Melnick–Needles osteodysplasty, and otopalatodigital syndrome type I (Table I). Other bone dysplasias in the literature that exhibit EFD-T are the Pyle-like entities which include Braun–Tinschert-metaphyseal dysplasia, Cantu syndrome, and multicentric fibromatosis with metaphyseal dysplasia (Table I). EFD-A was best illustrated by dysosteosclerosis and osteopetrosis (Table I) (Fig. 3). EFD-ME was seen in cases with Gaucher disease and Niemann-Pick disease. These cases are differentiated from skeletal dysplasias based on other organ system involvement, abnormal bone MRI and that the appendicular skeleton is primarily involved. In addition, bone marrow hyperplasia can result in similar metaphyseal expansion in thalassemia.

Table II summarizes the radiographic findings in these disorders. Among the 50 ISDR cases reviewed, there were 12 distinct disorders in which EFD was seen (Table III). We identified seven disorders with EFD-T, four disorders (dysosteosclerosis and osteopetrosis types) with EFD-A, and one disorder (Gaucher disease) with EFD-ME. In addition, there was a significant radiological variability related to the evolution of bone changes. As an example, the earliest onset of EFD we observed was in craniometaphyseal dysplasia at 7 months of age and those changes become more progressive and apparent with time. In some disorders thought to have EFD as a characteristic finding such as Gaucher disease, it was found that this was not a uniform finding.

DISCUSSION

An Erlenmeyer flask deformity evolves as the result of a modeling deformity arising in the metaphysis adjacent to the growth plate and with time extending into the diaphysis, a region we term the di-metaphysis or meta-diaphysis. In this analysis of the International Skeletal Dysplasia Registry (ISDR), EFD was identified in 12 distinct disorders and review of the literature increased the number of disorders with this finding to 20. The disorders are delineated below and discussed relative to the finding of EFD.

Craniotubular Bone Dysplasias

This group of disorders share variable degrees of cranial sclerosis and abnormal di-metaphyseal modeling of tubular bones. All of these disorders demonstrated EFD-T and in rarer conditions, EFD-A.

Frontometaphyseal Dysplasia [FMD; OMIM 305620]

This X-linked dominant disorder was first delineated by Gorlin and Cohen [1969], and results from mutations in the gene encoding filamin A. It is fully manifested in hemizygous males, and mildly in heterozygous females. The radiological findings are included in Table II [Gorlin et al., 1969; Danks et al., 1972; Medlar and Crawford, 1978]. The long and short bones are under modeled, with an EFD appearance mainly of the distal femora. We evaluated 11 cases and all showed EFD-T of the distal femora, basal and patchy sclerosis of the skull, and three (3/11) showed progressive scoliosis, however, carpal fusions were only seen in one case (1/11).

Otopalatodigital Syndrome, Type I [OPD I; OMIM 311300] and Osteodysplasty, Melnick–Needles Syndrome [MNS; OMIM 309350]

These are also X-linked dominant disorders due to mutations in the gene encoding filamin A [Robertson et al., 2003]. OPD types I and II, MNS syndromes, and FMD are the otopalatodigital syndrome spectrum disorders [Verloes et al., 2000] and share phenotypic findings [Robertson et al., 2003; Robertson, 2007]. The findings are included in Table I and they differ by the degreee of digital anomalies [Horn et al., 1995] and the presence contractures of the small joints of the hands in FMD. All these disorders share findings of a generalized bone disorder with di-metaphyseal flaring. In this study, five cases of MNS and two cases with OPD I were reviewed. All the cases of MNS and OPD I have EFD-T type.

Craniometaphyseal Dysplasia [CMD; OMIM 12300; 218400]

This craniotubular disorder has a very severe autosomal recessive form [Penchaszadeh et al., 1980] and a somewhat milder autosomal dominant form [Jackson et al., 1954; Spiro et al., 1975]. They are differentiated based on more generalized skull and diaphyseal involvement in the recessive form [Iughetti et al., 2000; Nurnberg et al., 2001]. Eleven cases were available for review (Table III). One case (1/11) showed severe modeling defects and EFD-T of only the distal femora, three cases showed progressive skull, and long and short bone changes that resulted in generalized EFD-T. The remainder of the cases (7/11) showed variable degrees of bone changes, ranging from mild to moderate metaphyseal and di-metaphyseal modeling defects [evolving EFD]. From our observations, bone changes became obvious as early as seven months of age and EFD-T was a uniform finding located in the appendicular skeleton.

Pyle Disease [OMIM 265900]

This disorder first described by Edwin Pyle [1931], then named familial metaphyseal dysplasia by Bakwin and Krida [1937]. The characteristic mild cranial sclerosis and the symmetric EFD of long bones are the hallmarks of the disorder. EFD is not confined to the distal femora, but also involves other long bones, mainly the proximal two-thirds of the humeri and tibiae, and

the distal two-thirds the radii and ulnae [Hsu et al., 1979]. Pyle disease has similarities to CMD, but differs clinically by the absence of cranial nerve compression, milder skull involvement, and more striking long bone modeling defects leading to typical EFD [Gorlin et al., 1969, 1970]. In this study, the one case available for review (Table III) showed EFD-T of all of the aforementioned long bones.

Other Metaphyseal Dysplasia—Pyle Like Entities

Numerous other entities that closely resemble MD-Pyle type have been delineated in the literature and review of the literature should that all were associated with EFD and should be considered in the differential diagnosis of metaphyseal dysplasias with EFD.

Metaphyseal Dysplasia, Braun–Tinschert Type [OMIM 605946]

This disorder has characteristic di-metaphyseal widening and under modeling of the tubular bones with EFD-T of the distal femora [Braun et al., 2001]. The hallmarks of the disorder include severe varus deformity of the radii, flat exostoses of the long bone metaphyses, and absence of any cranial sclerosis (Table I and Table II). Other radiographic findings are included in Table II [Takata et al., 2006].

Multicentric Fibromatosis With Pyle Dysplasia Bone Changes

Multicentric fibromatosis of the lower extremity had been reported in association with dysplastic changes and abnormal modeling of the long bones, similar to Pyle disease and show typical EFD [Disler et al., 1993]. It has been hypothesized that the underlying biology in this disorder results from mesenchyme that is predisposed to the development of both dysplastic bone changes and tumor.

Hypertrichotic Osteochondrodysplasia or Cantu Syndrome [OMIM 239850]

The major clinical and radiographic findings are listed in Table I and Table II [Cantu et al., 1982;Robertson et al., 1999;Concolino et al., 2000;Engels et al., 2002]. The EFD-T deformities involve the long bones (femora, humeri, radii, and ulnae) [Robertson et al., 1999].

Craniometadiaphyseal Dysplasia, Wormian Bone Type [CMDD; OMIM 269300]

This rare entity has been described previously as Schwartz–Lelek syndrome [MIM 269300] [Schwartz, 1960]. Subsequently, Williams [1988] and Langer et al. [1991] described a newly recognized craniotubular bone disorder. This disorder has typical EFD with cranial wormian bones. They postulated that the case previously reported by Schwartz [1960] had the same disorder and renamed the entity, craniometadiaphyseal dysplasia, wormian bone type.

Craniodiaphyseal Dysplasia [CDD, OMIM218300]

This is a severe bone dysplasia is characterized by marked hyperostosis and sclerosis of the skull and facial bones (Table II) [Gorlin et al., 1969]. In addition, there is extreme asymmetric hyperostosis and sclerosis of the “diaphyses” in the autosomal recessive form [Sydney, 1949], and evidence of a modeling defect in the di-metaphyses in the dominant form (Table II) [Schaefer et al., 1986]. The cohort review identified a single case with EFD-T in the distal femora. Even though this disorder is a diaphyseal one, under modeling of the di-metaphyses was seen and this is a novel finding in this rare disorder.

Diaphyseal Dysplasia-Engelmann Type, Camurati–Engelmann Disease [DD-E; OMIM 131300]

This disorder was delineated by Camurati [1922] and Engelmann [1929]. Subsequently termed Engelmann’s disease, or Camurati–Engelmann disease [Sears, 1948; Lelek, 1961], since has been used. The clinical and radiological findings [Makita et al., 2000] are listed in Table I and

Table II, respectively. Of the three cases identified in the cohort study only one showed EFD thus, a variable finding in this disorder.

Oculodentoosseous Dysplasia [ODOD; OMIM 164200]

Gorlin et al. [1963] described this condition using the designation oculodentodigital dysplasia [ODOD] [Littlewood and Lewis, 1963; Rajic and De Veber, 1966]. The long bones showed mild to moderate modeling defects and falls under the classification of EFD-T.

There have been numerous other single case reports on metaphyseal disorders with EFD. They include metaphyseal dysplasia with maxillary hypoplasia and brachydactyly [Halal et al., 1982], familial metaphyseal dysplasia with radial deformity [Hohle, 1982], metaphyseal dysplasia with hemimelic distribution [Polijvka, 1972], metaphyseal dysplasia-anectderma-optic atrophy [OMIM 250450] [Temtamy et al., 1974] and a syndrome of metaphyseal under modeling-spondylar dysplasia-overgrowth [Nishimura et al., 2004]. These reported entities are associated with EFD due to di-metaphyseal clubbing and cortical thinning, and fall under the classification of EFD-T.

EFD-A or EFD atypical was identified in two distinct sets of entities, dysosteosclerosis and the osteopetrosis disorders.

Dysosteosclerosis [MIM 224300] and Osteopetrosis [OMIM; 259700, 259720,166600, 259710]

Dysosteosclerosis is a rare bone dysplasia [Spranger et al., 1968; Elcioglu et al., 2002]. The early craniotubular bone involvement and clinical presentation has some similarities to osteopetrosis because of increased bone density and tendency to fracture. Yet, they differ clinically by the presence of neurodevelopmental regression and hepatosplenomegaly in dysosteosclerosis, and variable degrees of anemia and/or pancytopenia in the osteopetrosis disorders [Mohn et al., 2004] (Table I). Cranial sclerosis predominantly affects the base in dysosteosclerosis [Elster et al., 1992], while in the osteopetrosis disorders there is significant vault involvement. Dysosteosclerosis has a distinctive meta-diaphyseal bulbous expansion with alternating bands of sclerotic and normal bone density, while in osteopetrosis, the expanded di-metaphyseal areas are homogenously sclerotic and there is a characteristic bone-in-a-bone appearance of the long bones, pelvis, and spine (sandwich or Rugger Jersey appearance) [Bollerslev and Mosekilde, 1993; Senel et al., 2002]. Review of the cases in the literature and the ISDR revealed that patients with dysosteosclerosis and osteopetrosis uniformally have EFD-A with radiographically densely abnormal appearing bone (Table III).

Osteopetrosis With Renal Tubular Acidosis [OMIM 259730]

First described by Zackai et al. [1972] osteopetrosis with renal tubular acidosis, was further then delineated by Whyte et al. [1980]. Almost half of the reported cases were from Kuwait, North Africa, and Saudi Arabia, where it is referred to as marble brain disease [Ohlsson et al., 1980; Bourke et al., 1981]. It is a distinct form of osteopetrosis caused by defects in the gene encoding Carbonic Anhydrase II [Zackai et al., 1972; Whyte et al., 1980]. It shares radiographic findings with the other forms types of osteopetrosis, but differs by the presence of mild tubular acidosis, basal ganglion calcification during adolescence [Whyte et al., 1980] and mental and psychomotor retardation (Table I). In the two cases available, EFD-A was found in the distal femora.

Metabolic Disorders and Syndromes

The last group is EFD-ME type in which the bone marrow is expanded as a result of infiltration with abnormal storage material as in cases with Gaucher and Niemann-Pick diseases.

Gaucher Disease [GD; OMIM 230800]

GD is an autosomal recessive inherited disorder caused by deficient activity of beta-glucocerebrosidase. The non-neuropathic type (type I) is the most common form of GD and clinical findings are listed in Table I and Table II. The clinical manifestations result from progressive accumulation of lipid glucocerebroside in the lysosomes of monocytes and macrophages that infiltrate organs including bone, leading to expansion [Goldblatt et al., 1978;D'Arena et al., 2001;Wenstrup et al., 2002]. The exact mechanisms causing the high rates of bone turnover and failure of remodeling are not well understood [Butora et al., 1989;Barak et al., 1999]. In the six cases reviewed, only three demonstrated EFD-ME and thus was not a uniform finding (Table III).

Niemann-Pick Disease, Type B [NPD-B;OMIM 607616]

NPD disease is heterogeneous group of lysosomal storage disorders. Type B NP (visceral type) results from sphingomyelin accumulation in various tissues (foamy histiocytes in liver, spleen, bone marrow, adrenal medulla, and lymph nodes) secondary to acid sphingomyelinase deficiency. Recurrent pneumonia from interstitial lung infiltration and progressive decline in pulmonary function are major contributors to morbidity and mortality [Minai et al., 2000; Candoni et al., 2001]. The primary bone changes are progressive medullary cavity expansion of the distal femora similar to that in GD [Lachman et al., 1973], a thumbprint effect (dome sign) marrow cavity expansion of the proximal femora, and metacarpal widening. Review of the literature showed that EFD-ME was not uniformly seen in the distal femora and in one case, the proximal humerus [Crocker and Farber, 1958; Gildenhorn and Amromin, 1961].

Membranous Lipodystrophy or Polycystic Lipomembranous Osteodysplasia With Sclerosing Leukoencephalopathy [PLOSL; OMIM 221770]

This rare hereditary disorder is characterized by the appearance of polycystic bone lesions, followed later by neuropsychiatric symptoms around the third decade [Madry et al., 2007]. Radiographic changes are listed in Table II and an Erlenmeyer flask deformity sometimes develops in the long bones (distal femora, proximal humeri, tibiae, and fibulae) with scalloping of the endosteal aspect of the cortex [Akai et al., 1977; Makela et al., 1982]. The main pathogenic mechanism is not known, but some have suggested vascular changes associated with the membranocystic lesions which also cause severe chronic vasogenic brain edema [Ahn et al., 1996; Bianchin et al., 2004]. Review of the radiographs of patients in the literature showed that all have EFD-ME type.

Thalassemia [OMIM 187550] and Desferroxamine-Induced Bone Dysplasia

Beta-thalassemia is multisystemic inherited single gene disorder first described by Cooley et al. [1927] and results from reduced to absent β-globin chain synthesis. Consequently, ineffective haematopoiesis causes severe anemia and significant extramedullary hematopoiesis with secondary skeletal deformity [Wonke, 1998]. The femurs develop a flask like shape with irregular transverse radiolinear lines at the ends of the long bones representing growth arrest and recovery lines [Tyler et al., 2006] (Table II). The findings of cases reviewed in the literature are consistent with EFD-ME. Patients with thalassemia, especially those treated with DFO either at less than 3 years of age or with high doses, can manifest a DFO skeletal dysplasia with platyspondyly, metaphyseal irregularity/sclerosis, radiolucent di-metaphyses producing EFD [Lachman, 2007].

Lead Poisoning

Lead poisoning has been described as producing EFD of the long bones. Review of the literature showed that the lead induced lesion is confined to an increased metaphyseal radiodensity of the long bones. As interpreted by Eisenstein and Kawanoue [1975], the lead line is a result of

persistent mineralized metaphyseal cartilage and not to a primary osseous change. It has been mentioned that in some long standing cases, the metaphyseal ends of the long bones become clubbed from lack of modeling, and resemble the appearance of EFD [Blickman et al., 1986; Kosnett et al., 2007; Lachman, 2007]. However, our review of the published radiographic figures would not classify the changes as consistent with EFD of any type.

Fetal Magnesium Toxicity

This entity was first reported by Lamm et al. [1988] long term exposure to IV magnesium sulphate ($MgSO_4$) in utero for tocolysis resulted in development of neonatal bone abnormalities. It was proposed that hypermagnesemia suppressed fetal parathyroid function and induced fetal hypocalcemia. It also inhibits calcification of osteoid directly by competition of magnesium with calcium. The skeletal abnormalities that are recognized at birth (Table I). EFD of the distal femora, and fractures of the long bones are seen [Wedig et al., 2006]. It radiographically differs from rickets of prematurity by the preserved provisional zones of calcification. Appropriate nutritional support of the newborn with magnesium sulfate toxicity reverses the bone changes and improves bone mineralization.

In conclusion, when an Erlenmeyer flask deformity is seen on radiographic analysis, the differential diagnosis should include the disorders listed above and differentiated based on the clinical and radiographic findings delineated in Table I and Table II. The presence of radiographically normal appearing trabecular bones strongly suggests that the findings are associated with the craniotubular disorders, especially if there is no evidence of metabolic disease. EFD with abnormal appearing trabecular bone is highly suggestive of dysosteosclerosis and the osteopetrosis disorders. The location of the EFD is not necessarily always the femora and can be seen in the other long bones. Further, the onset of the finding is not uniform and can progress with time. Lastly, it can be absent in some disorders in which it is considered characteristic and thus, its absence does not necessarily exclude a disorder.

Acknowledgments

This work is supported by NIHCDHD22567 to DLR, DK and RSL. DK is also supported by the Drown Foundation and the Winnick Family Scholar Fund. MF would like to thank Dr. Hamad Al-Mane at the Ministry of Health of Saudi Arabia for funding her fellowship at Cedar Siani Medical Center. The authors would like to thank the referring physicians and patients for their participation. We would also like to thank MaryAnn Priore and Arleen Hernandez for their administrative contributions to this study.

Grant sponsor: NIHCD; Grant Number: HD 22567.

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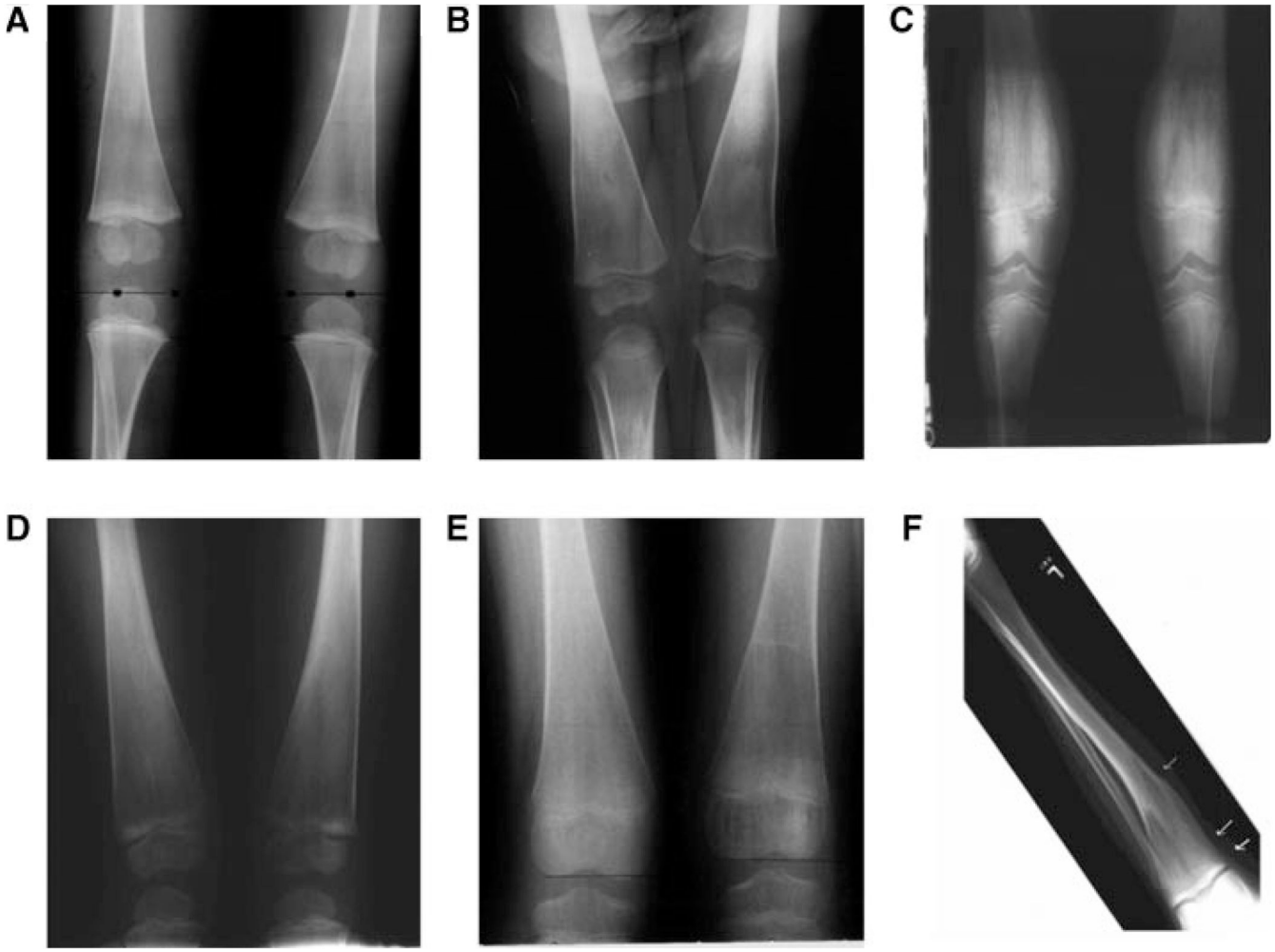

FIG. 1.

Radiographs of distal femora. A: EFD-T of the distal femur with normal bone trabeculae. B: Normal distal femur. For both (A,B) the arrows from the top down indicate the diaphysis, the di-metaphyseal region, and the metaphysis.

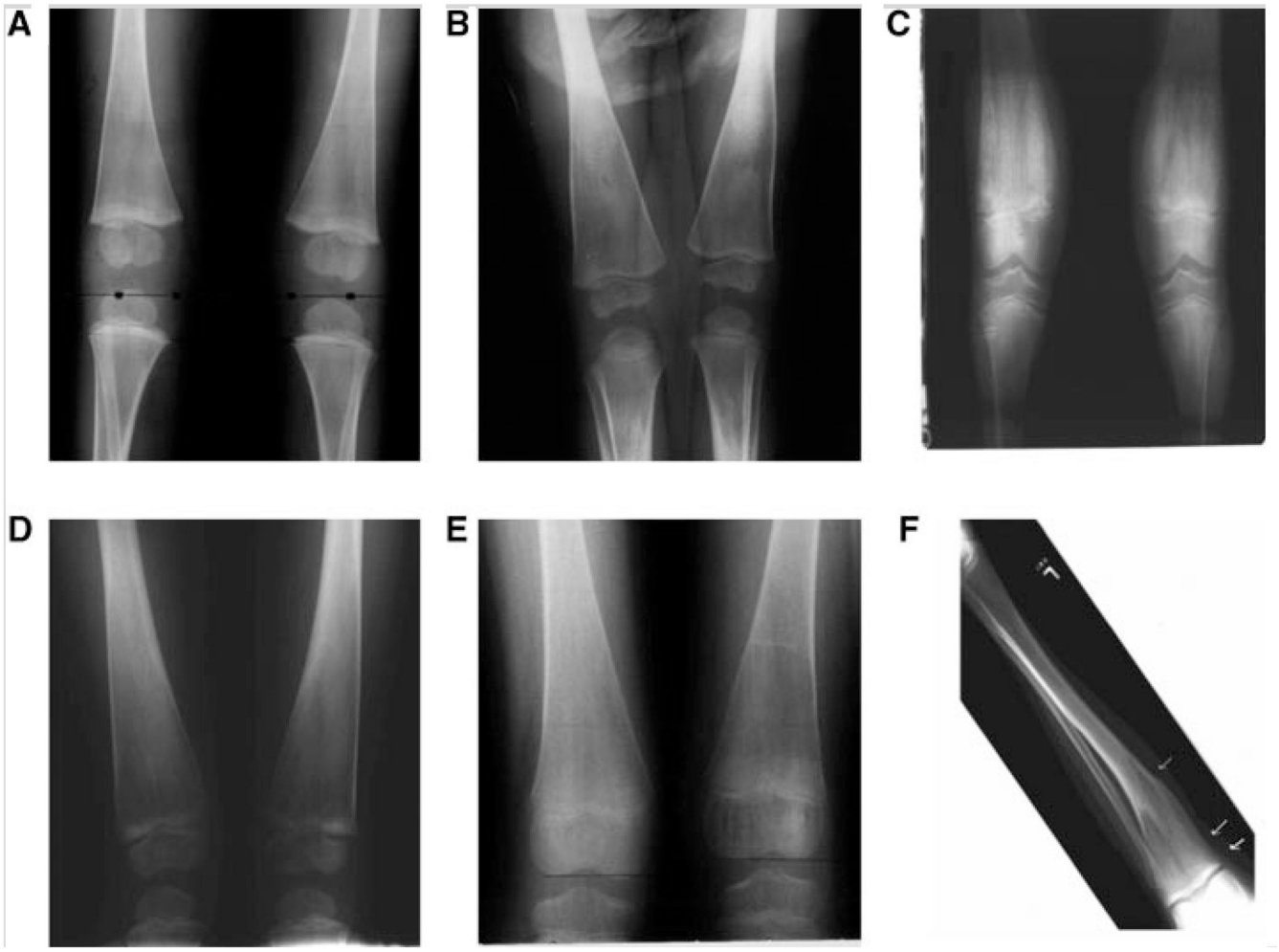

FIG. 2.

EFD-T type of the ditstal femora. Note the normal appearing bone trabeculae. A: Frontometaphyseal dysplasia. B: Craniometaphyseal metaphyseal dysplasia. C: Metaphyseal dysplasia—Pyle type. D: Craniodiaphyseal dysplasia. E: Otopalatodigital syndrome, Type I. F: Melnick–Needles syndrome (inverted image, EFD of proximal end of the tibia).

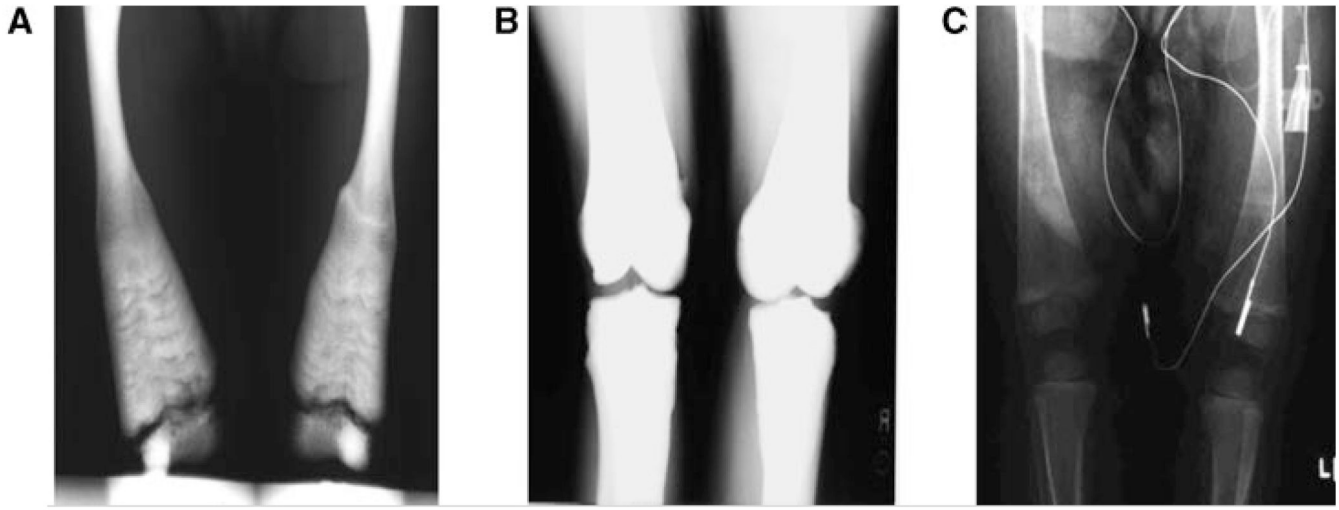

FIG. 3.
EFD-A type (A,B) and EFD-ME type (C) of distal femora. A: Dysosteosclerosis. B: Osteopetrosis. C: Gaucher disease. Note the abnormal bone trabeculae (A,B) and normal bone trabeculae (C).

TABLE I

Cranio-Tubular Bone Dysplasias

Diseases	Inheritance pattern	Gene	Clinical manifestations
Cranio-tubular bone dysplasias			
Frontometaphyseal dysplasia	X-LR	*FLNA*	Males; dysmorphic facies, dental anomalies, deafness, hirsutism, muscle wasting, large and small joints contractures, renal and respiratory abnormalities. Females: milder manifestations
Craniometaphyseal dysplasia	AD, AR	*ANKH* (dominant), 6q21–22 (recessive)	Facial dysmorphism, dental anomalies, progressive cranial nerve compression (deafness, optic atrophy and facial nerves paralysis), respiratory abnormalities, hemiplegia, quadriplegia
Craniodiaphyseal dysplasia	AD, AR	Unidentified	Progressive cranial nerve impingement, obliteration of paranasal sinuses, facial diplegia, hearing and vision loss, mental retardation, respiratory difficulties, recurrent dacrocystitis
Craniometadiaphyseal dysplasia	AR	Unidentified	Facial dysmorphism, macrocephaly, large eyes, antimongloid slanting palpebral fissures, malar hypoplasia, high arched palate, mild prognanthism, dental hypoplasia
Diaphyseal dysplasia, Engelmann type	AD	*TGFB1*	Mild facial dysmorphisms, exophthalmous, progressive cranial nerve impingement, failure to thrive, thin habitus, muscle weakness, leg pain
Oculodentoosseous dysplasia	AD	*GJA1*	Facial dysmorphisms, thin nose, hypoplastic ala, narrow nostrisl, hypertelorism, microcornea, enamel hypoplasia, syndactyly of 4,5 digits, spastic paresis
Metaphyseal dysplasia, Pyle type	AR	Unidentified	No craniofacial dysmorphisms, no cranial nerve compression, dental malocclusions, muscle weakness, joint pain, limited elbow extension
Dysosteosclerosis	AR, X-LR	Unidentified	Short stature, narrow mid-face, dental anomalies, cranial nerve compression (progressive vision loss, facial paralysis, hearing loss), neuron-developmental regression, seizures, red violet macular atrophy of skin

Diseases	Inheritance pattern	Gene	Clinical manifestations
Osteodysplasty, Melnick–Needles	X-LD	*FLNA*	Males: lethal. Females: facial dysmorphism (full cheeks, exophthalmous), dental anomalies, short distal phalanges
Pyle like entities			
Braun–Tinschert MD	AD	Unidentified	No craniofacial dysmorphisms, premature loss of primary teeth, limited shoulder internal rotation, forearm deformities, scoliosis, exostoses at metadiaphyses
Hypertrichotic osteochondrodysplasia (Cantu syndrome)	AD, sporadic	Unidentified	Coarse dysmorphic facies (prominent forehead, broad nasal bridge, hypertelorism), hypertrichosis, CHD (cardiomegaly, PDA, valve abnormalities), narrow thorax, umbilical hernia
Multicenteric fibromatosis with MD	Unknown	Unidentified	Recurrent multicentric fibromatosis (extremities, mainly thigh and peritibial areas, posterior ileum)
Osteopetrosis			
Infantile osteopetrosis	AR	*TCIRG1*, *CLCN7*, *OSTMI*	Macrocephaly, hydrocephaly, optic nerve atrophy, facial paresis, delay dentition, failure to thrive, psychomotor retardation, anemia/pancytopenia, hepatosplenomegaly severe prenatal form: stillborns reported
Juvenile osteopetrosis (Type II, III)	AD(II), AR (III)	*CLCN7* (*II*)	Poor dentition, vision and hearing defects, facial paresis, anemia, hepatosplenomegaly, osteomyelitis of mandible and maxilla
Osteopetrosis with renal tubular acidosis	AR	*CA II*	Mild facial dysmorphisms, dental abnormalities, mental retardation, renal tubular acidosis, learning disability. Less frequent: cranial nerve compression, hypokalemic paralysis
Metabolic disorders and syndromes			
Gaucher disease Type I	AR	*GBA*	Hepatosplenomegaly, anemia, pancytopenia, interstitial lung disease, pulmonary hypertension, bone pain, pathologic fractures, nephrotic syndrome
Niemann-Pick disease Type B	AR	*SMPD1*	Cherry-red maculae, hepatosplenomegaly, pancytopenia, blue histiocytic cells within the bone marrow, frequent respiratory tract infections

Diseases	Inheritance pattern	Gene	Clinical manifestations
Membranous lipodystrophy	AR	*TYROBP*; *TREM2*	Bone pain, painful swelling of ankles and wrists after stress or injury, membranous lipodystrophic changes, progressive neuro-psychiatric abnormalities and seizures
Otopalatodigital syndrome, Type I	X-LD	*FLNA*	Facial dysmorphisms, dental abnormalities, cleft palate, hearing loss, limited elbow extension and knee flexion. Female: milder form
Other entities			
Thalassemia	AR	Beta-globin gene deletion	Coarse face, anemia, jaundice, hepatosplenomegaly, cholelithiasis, hematuria, extramedullary haematopoiesis with secondary skeletal deformity

AD, autosomal dominant; AR, autosomal recessive; X-LR, X-linked recessive; X-LD, X-linked dominant; CHD, congenital heart disease; MD, metaphyseal dysplasia; *FLNA*, filamin A; *ANKH*, progressive ankylosis gene; *TGFB1*, transforming growth factor β1; GROWTH, *GJA1*, gap junction protein α-1; *CLCN7*, chloride channel *7* gene; CA II, carbonic anhydrase gene; *GBA*, acid beta-glucocerebrosidase gene; *OSTMI*, osteopetrosis-associated transmembrane protein-1; *TCIRG1*, T cell immune regulator gene 1; OSTM1, osteopetrosis-associated transmembrane protein 1; *SMPD1*, sphingomyelin phosphodiesterase-1 gene; *TYROBP*, tyro protein tyrosine kinase-binding protein; *TREM2*, triggering receptor expressed on myeloid cells 2.

TABLE II

The Radiological Findings of Literature Entities With EFD

Disease	Cranium	Chest	Spine	Pelvis	Long tubular bones	Short tubular bones
Frontometaphyseal dysplasia	Thick frontal ridge, absent frontal sinus pneumatization, variable patchy skull sclerosis	Irregular rib contours, coat hanger deformities of lower ribs	Scoliosis, increased IPD of lumbar vertebrae, cervical vertebral fusion	Marked flaring of iliac wings, coxa valga	Hyperdense diaphyses, EFD of femora	Long under-modeled MTC, MTT, and Ph, carpal bone fusions
Craniometaphyseal dysplasia	Sclerosis of cranial vault, base and facial bones with cranial foraminal narrowing, ground-glass mandible, sinus obliteration	Wide ribs and clavicles	Normal	Normal	Early diaphyseal sclerosis; later, MF widening and EFD of femora	Normal to mild metaphyseal modeling defect
Craniodiaphyseal dysplasia	Macrocephaly, progressive craniofacial bone thickening, cranial foraminal obliteration, obliteration of paranasal sinuses, marked prognathism, hydrocephalus	Extensive sclerosis and widening of clavicles and ribs	Cervical vertebral sclerosis, increase neural arch density	Marked sclerosis	Diaphyseal sclerosis and widening, thicked diaphyseal cortex; in AD type, metaphyseal modeling defect with thin cortices; EFD of the distal femora	Diaphyseal sclerosis, thickening and widening
Cranio-meta-diaphyseal dysplasia	Marked decrease ossification, mild skull base and orbital sclerosis, multiple wormian bones, paranasal sinus and mastoid obliteration, occipital horns	Wide flared clavicles and ribs	Wide, osteopenic posterior arches of cervical and dorsal vertebrae, mild scoliosis	Narrow pelvis, broad ischia, coxa valga	Undermodeled LTB with poor MF, short mid-diaphyses with under-modeling, increased metaphyseal density, mild femoral bowing and EFD	Widened with osteopenia, lack of normal diaphyseal constriction, thin cortices, MTC-pseudoepiphyses
Diaphyseal dysplasia, Engelmann type	Sclerosis of skull base, vault and facial bones, narrowing of nerve and vessel foramina	Normal	Sclerosis of posterior part of vertebrae especially cervical region, scoliosis	Normal	Progressive diaphyseal widening and thickened cortices, narrow medullary canal, EFD	Diaphyseal widening and thickened cortices
Oculo-dento-osseous dysplasia	Wide alveolar ridge and body	Mild widening of the ribs and clavicles	Normal or platyspondyly	Normal to mild sclerosis	Mild to moderate widening of almost the	Widened, camptodactyly of

Disease	Cranium	Chest	Spine	Pelvis	Long tubular bones	Short tubular bones
	of the mandible, obtuse mandibular angle				entire shaft	3,4,5 digits, hypoplastic middle Ph; absent middle toe Ph
Metaphyseal dysplasia, Pyle type	Mild cranial base and vault sclerosis, prominent supraorbital ridges, poor mastoid paranasal sinus pneumatization, mild proganthism	Thickened ribs and clavicles	Scoliosis, mild/moderate platyspondyly, cod-fish vertebral bodies	Thickened ischiopubic bones	Marked modeling defects, EFD mainly distal femora, proximal humeri and tibiae, distal ulnae and radii, S-shaped tibia	MF of MTC distally and Ph proximally
Braun–Tinschert metaphyseal dysplasia	Not described	Not described	Not described	Not described	Metaphyseal widening of distal femora (EFD), proximal tibiae, distal radii and ulnae, varus deformity of the distal radii and/or proximal humeri, bowing of the ulnae and fibulae, exostosis at the di-metaphysis	Cortical osteosclerosis in the metaphyses of the MTC and proximal and middle Ph
Osteodysplasty, Melnick–Needles	Sclerosis of the cranial base and mastoids, delayed AF closure, micrognathia with hypoplastic coronoid process of mandible, wide angle between mandibular rami, cystic mandibular rami	Ribbon like ribs with cortical irregularities, Flared clavicles, delayed sternal ossification, pectus excavatum	Tall vertebrae, anterior concavity of thoracic vertebrae, kyphoscoliosis	Narrow supra-acetabular portion of iliae with mild iliac flaring, flat acetabular roofs	Metaphyseal flaring, long femoral neck, subtrochanteric narrowing, coxa valga, S-shape bending of ulnae, radii and tibiae, genu valgum	Shortened distal phalanges, cone-shaped epiphyses
Hypertrichotic osteochondrodysplasia (Cantu syndrome)	Thickened diploic space and vertical skull base, enlarged sella turcica	Narrow thorax and widened ribs	Platyspondyly, ovoid vertebral bodies, vertebral endplate irregularities	Hypoplastic ischio-pubic rami, coxa valga, narrow obturator foramina	Widened metaphyses with enlarged medullary canal, EFD of LTB, bands of metaphyseal growth arrest	Broad first metatarsal
Dysosteosclerosis	Sclerosis of the skull base and mastoids, intracerebral calcifications, absent pneumatization of	Sclerosis of ribs, clavicles, sternum and scapulae	Platyspondyly, sclerotic vertebral bodies with dorsal wedging	Sclerotic pelvic bone with iliae hypoplasia	Club-shaped bones with thin cortices, EFD of femora, metaphyseal echodense lines adjacent to echolucent diaphyses	Sclerotic metaphyseal margins, phalangeal tuft resorption

Disease	Cranium	Chest	Spine	Pelvis	Long tubular bones	Short tubular bones
	paranasal sinuses and mastoids					
Infantile osteopetrosis	Sclerosis of cranial base and vault, mastoid and paranasal sinus under pneumatization, progressive neural and vascular foraminal narrowing	Increased bone density	Sandwich vertebrae with bone in bone appearance	Sclerosis of the central portions of pelvis and femora, coxa vara	Homogenous increase in bone density, club-shaped metaphyses, echolucent band at metaphyseal ends; later, bone in bone appearance, pathologic fractures	Metaphyseal echolucent transverse lines
Juvenile osteopetrosis (Types II, III)	*Type II*: cranial base sclerosis, minimal cranial vault involvement, normal sinuses *Type III*: moderate cranial base and vault sclerosis	Increased bone density	*Type II*: ''rugger-jersey'' vertebrae *Type III*: severely increased density of the upper and lower end plates	*Type II*: diffuse increased bone density, hip osteoarthritis. *Type III*: sclerotic bands in the iliac wings parallel to the crests	*Type II*: bone within bone, sclerosis of femoral neck, metaphyseal clubbing, fractures *Type III*: marked metaphyseal clubbing of the femora with alternating areas of increased and normal bone density, diaphyseal sclerosis, fractures, genu valgum	Areas of sclerosis and normal bone density in carpal and tubular bones
Osteopetrosis with renal tubular acidosis	Sclerotic thick skull base, obliteration of paranasal sinuses and mastoids, cerebral calcifications	Widening of the anterior ribs	Sandwich vertebrae	Bone within bone appearance with arcuate striations of iliae	Generalized sclerosis, bone within bone appearance, poor corticomedullary definition, defective metaphyseal modeling	Bone within bone appearance, defective metaphyseal modeling
Multicenteric fibromatosis with MD	Not described	Not described	Not described	Shallow acetabulae, short femoral necks	Metaphyseal widening, of proximal tibiae, humeri and distal femora, cortical thinning	Not described
Gaucher disease Type I	Cystic lesions	Thin deformed ribs	Vertebral collapse with spinal cord compression	Cystic lesions	EFD of distal femora, avascular necrosis of femoral heads, moth-eaten appearance of bones, pathologic fractures	Cystic lesions
Niemann-Pick disease Type B	None	None	Notched lumbar vertebrae	Osteoporosis, anterior vertebral notching, fractures, coxa valga	Modeling defects and thin cortices, notch defects of the proximal humeri	Widened metacarpals with thin cortices

Disease	Cranium	Chest	Spine	Pelvis	Long tubular bones	Short tubular bones
Membranous lipodystrophy	Not described	Not described	Not described	Not described	Symmetrical radiolucent cystic changes in the metaphyses, diaphyses, and patella, EFD, pathologic fractures	Bone cysts in hands and feet
Otopalatodigital syndrome, Type I	Thick frontal bone and skull base sclerosis, steep clivus, dense middle-ear ossicles, poor mastoid development, absent frontal and sphenoid sinuses, small mandible	Pectus excavatum	Scoliosis, small pedicles, posterior defect of neural arches, widened lower thoracic and lumbosacral spinal canal	Small iliac crests, hip dislocations, flat acetabulae, coxa valga	Radial head dislocations, mild, lateral femoral bowing	Carpal bone anomalies, especially fusions
Thalassemia	Diploic space expansion, lytic lesions, paranasal sinus hypoplasia, dental displacement and deformaties	Osteopenia, coarse bony trabeculae, cortical thinning, rib-within-rib appearance, clavicular and costal widening, rib notching	Biconcave vertebral configuration (cod-fish vertebrae), scoliosis, compression fractures, bone-within-bone appearance	Medullary hyperplasia of the pelvis	Widened medullary cavity with cortical thinning, premature growth plate closure, EFD of distal femora, aseptic femoral head necrosis	Osteoporosis, coarse trabeculation, widened tubular bones of hands and feet

EFD, Erlenmeyer flask deformity; AF, anterior fontanel; MTC, metacarpals; MTT, metatarsals; Ph, phalanges; IPD, interpediculate distance; LTB, long tubular bones; MF, metaphyseal flaring.

TABLE III

Cases Available in the ISDR

Disorder	# cases # cases with EFD	EFD-T	EFD-A	EFD-ME	
Frontometaphyseal dysplasia	11	11/11	*		
Craniometaphyseal dysplasia	11	4/11	*		
Metaphyseal dysplasia, Pyle type	1	1/1	*		
Craniodiaphyseal dysplasia	1	1/1	*		
Diaphyseal dysplasia, Engelmann type	3	1/3	*		
Osteodysplasty, Melnick–Needles	5	5/5	*		
Dysosteosclerosis	3	3/3		*	
Infantile osteopetrosis	2	2/3		*	
Juvenile osteopetrosis	3	3/3		*	
Osteopetrosis with renal tubular acidosis	2	2/2		*	
Otopalatodigital syndrome, Type I	2	2/2	*		
Gaucher disease Type I	6	3/6			*
Total	50				

cases; available cases for review in the ISDR; EFD, Erlenmeyer flask deformity.