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Skeletal Manifestations of Inborn Errors of Metabolism: A Comprehensive Retrospect

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Inborn errors of metabolism encompass a wide variety of disorders, frequently affecting bone. This review presents a comprehensive retrospect on the primary involvement of bone in inborn errors of metabolism. Primary involvement of bone in inborn errors of metabolism includes entities that primarily affect the bone marrow, mineral component or cartilage. These include lysosomal storage disorders, hypophosphatasia, and hereditary hypophosphatemic rickets. In this review, we discuss the primary involvement of bone in inborn errors of metabolism (hypophosphatasia, X-linked hypophosphatemic rickets, Gaucher disease, and mucopolysaccharidoses) along with the therapeutic agents used in clinical settings, diagnostic strategies, and general management. With the development of disease-specific targeted therapies and supportive care, more number of patients with these disorders live longer and survive into adulthood. Moreover, skeletal symptoms have become a more prominent feature of these disorders. This makes the awareness of these skeletal symptoms more important.

Key words: Inborn errors of metabolism, bone, hypophosphatasia, X-linked hypophosphatemic rickets, Gaucher disease, mucopolysaccharidoses

Introduction

The skeletal system is frequently affected by inborn errors of metabolism. Some disorders, such as mucopolysaccharidoses (MPSs), primarily affect the bone and present with prominent skeletal features. On the other hand, in other disorders, alterations such as low bone mass may present secondary to nutritional deficiencies as a consequence of strict diets, inflammation, hypogonadism, and/or medications, especially anti-epileptic drugs[1]. This review presents a comprehensive retrospect on primary involvement of bone in inborn errors of metabolism. This group includes entities such as lysosomal storage disorders, hypophosphatasia (HPP), and hereditary hypophosphatemic rickets that primarily affect the bone marrow, mineral component or cartilage (Table 1). Secondary involvement of bone in inborn errors of metabolism mainly include disorders of amino acid metabolism, such as phenylketonuria and homocystinuria (Table 2). In this review, we discuss the primary involvement of bone in inborn errors of metabolism along with the therapeutic agents used in clinical settings, diagnostic strategies, and general management.

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Diagnostic clues

Inborn errors of metabolism manifest as skeletal deformities, retarded growth, or both in children. On the contrary, adults more frequently exhibit subtle deformities, pain, or fractures as initial symptoms of an underlying metabolic defect. Therefore, diagnosis may be delayed in patients with attenuated phenotypes. The recent advent of genetic screening techniques, such as whole-exome sequencing, have shortened the time to diagnosis. However, clinical, biochemical, and radiological findings are still required to arrive at an accurate diagnosis[2]. The diagnostic clues for inborn errors of metabolism are shown in Tables 1 and 2.

Clinical signs and symptoms

MPSs are a group of rare lysosomal storage disorders caused by inherited defects in the catabolism of sulfated components of connective tissue known as glycosaminoglycans. These group of disorders manifest as skeletal dysplasia and dysostosis multiplex. It may also present as the first sign of an attenuated phenotype[3]. Early arthropathy is the primary and most common skeletal symptom of mucolipidoses (MLs). Joint stiffness and carpal tunnel syndrome are frequent symptoms of ML III, which resemble the features of MPS I and VI. In patients with mild MPS, hand arthropathy may mimic rheumatological disease[4]. Although splenomegaly or cytopenia are the first symptoms in most cases of

Table 1. Inborn errors of metabolism primarily affecting the bone

Disease	Symptoms	Laboratory findings
Hereditary hypophosphatemic rickets	Short stature, lower extremity deformities;	decreased plasma phosphate
Hypophosphatasia	infantile : respiratory distress, hypotonia older : rachitis-like features, chronic pain, recurrent fractures	decrease plasam bone specific alkaline phophatase
Gaucher disease type 1 or 3	Bone pain, bone crises, pathological fractures, avascular necrosis, osteoporosis, Hepatosplenomegaly	cytopenia cytopenia
Niemann Pick A/B	arthritis, osteopenia, hepatosplenomegaly, interstitial lung disease	
MPSs	dysostosis multiplex, short stature, joint stiffness, or laxity (MPS IV), facial dysmorphism, hernias (MPSes), corneal clouding, carpal tunnel syndrome, ENT problems, cognitive decline	increased GAGs, specific enzyme deficiency
Pycnodysostosis	osteoporosis, short stature, pathological fractures	
Mannosidosis	dysostosis multiplex, psychiatric symptoms, corneal clouding or cataract, hearing loss, immune deficiencies, myopathy	accumulation of mannose-rich oligosaccharides
Alkaptouria	progressive deformation of the spine and arthrosis of the large joints, genitourinary tract stones, cardiac valve disease, dark urine, pigmentation of the auricle and sclera	accumulation of homogentisic acid and benzoquinone acetic acid in urine

Table 2. Inborn errors of metabolism with secondary bone disease

Disease	Symptoms
All inborn errors of metabolism that require strict dietary treatment	Miscellaneous; frequently neurological symptoms
Galactosemia	Cognitive impairment, primary ovarian failure, cataract
Phenylketonuria	Cognitive impairment in untreated patients
Homocystinuria	Marfanoid habitus, kyphosis, lens luxation, cognitive impairment
Lysinuric Protein Intolerance	Protein avoidance, gastrointestinal symptoms hyperammonaemia, lung disease
Wilson disease	Liver disease and / or neurological and psychiatric manifestations
GSD type II (Pompe disease)	Muscle weakness, secondary respiratory impairment

Gaucher disease (GD), patients may seek medical attention due to skeletal problems. Patients with GD may present with pain as the first symptom. Severe bone crises and avascular necrosis of the femoral head may occur in these patients[5]. Erlenmeyer flask deformity of the femur is a typical radiographic feature of GD. Pathological fractures have been reported in patients with GD and pycnodysostosis. Skeletal manifestations are less prominent; however, arthropathy may occur due to acid sphingomyelinase deficiency. In hypophosphatasia, arthropathy is common, and chronic pain may result from myopathy[6]. Spinal abnormalities, like pathological fractures, bone crises, kyphosis can be encountered in patients with GD. Contrarily, dysplasia, kyphosis and scoliosis are the spinal abnormalities commonly found in patients with MPSs. Osteoporosis is unlikely to be a presenting symptom. Thus, in patients with joint stiffness, early arthropathy, arthritis with negative rheumatoid factor, femoral head necrosis, unexplained bone pain, and radiographic evidence of bone deformities, especially in the presence of other features such as growth retardation, underlying metabolic disorders should be considered as a differential diagnosis.

Biochemistry

Very low levels of bone-specific alkaline phosphatase (ALP) are good indicators of HPP. Hypophosphatemia and low levels of normal circulating 1,25-dihydroxy vitamin D [1,25(OH)2D] levels are typical biochemical findings in hereditary hypophosphatemic rickets. Low 25-vitamin D and elevated ALP levels can be easily mistaken for vitamin D deficiency in patients with mild phenotypes. Routine biochemistry results are usually normal in other metabolic disorders that present with skeletal features.

Diagnosis

Enzymatic testing is the gold standard for diagnosing lysosomal storage disorders. Appropriate genetic testing should always be performed to confirm the diagnosis of metabolic disorders. Furthermore, genetic counseling is essential to identify other affected family members and predict disease prognosis.

Specific diseases

1. Hypophosphatasia

HPP is a genetic disease caused by biallelic loss-of-function of Alkaline Phosphatase, Biomineralization Associated (ALPL) variants or a heterozygous ALPL variant with dominant-negative effect. ALPL encodes an enzyme, tissue-nonspecific alkaline phosphatase (TNSALP), which hydrolyzes extracellular inorganic phosphates, a potent mineralization inhibitor, to enable the physiological deposition of hydroxyapatite in bones and teeth. TNSALP also converts pyridoxal 5'-phosphate (PLP) to pyridoxal (PL) to facilitate passage of the active metabolite of vitamin B6 through the cell membranes[7]. Inorganic pyrophosphate is an inhibitor of bone and tooth mineralization, and PLP is involved in neurotoxicity. The most common skeletal symptoms of HPP include rickets, bone pain, and fractures. Muscle hypotonia can result in walking problems. Hypotonia and respiratory distress can lead to early death in perinatal and infantile patients. Children frequently exhibit growth retardation and develop craniosynostosis. Adults may also experience fragile fractures and chronic pain [8]. HPP is classified into six subtypes on the basis of symptom onset and severity of manifestations: perinatal lethal, perinatal benign, infantile, childhood, adult, and odontohypophosphatasia.

Radiographic and dental features of HPP include:

-Prenatal long bone bowing with osteochondral spurs
-Infantile rickets: under mineralized bones, flared metaphyses, poorly ossified epiphyses, bowed long bones, widened sutures, and rachitic costochondral rib changes.
-Multiple tongue-like radiolucencies in the metaphyses
-Premature loss of deciduous teeth

Conservative treatment for HPP includes periodontal and dental care, sufficient physical activity, and orthopedic interventions. Subcutaneous asfotase alfa (Strensiq®), a first-in-class bone-targeted human recombinant TNSALP replacement therapy, was introduced in Korea in 2016 and is now available in several countries. It has been reported that asfotase alfa can improve rickets in this group of patients, which was proven by an improvement in radiographically assessed severity scores at 24 weeks[9]. Furthermore, patients experienced improvements in respiratory function, gross motor function, fine motor function, growth, and quality of life[10]. The 6-year outcomes of two children with infantile and perinatal lethal HPP after estrogen replacement therapy (ERT) has been described in our previous report[11]. Although clinical improvements were noted in both patients, there were differences in clinical features and treatment courses between the two patients (Fig. 1). Age at the time of commencement of ERT and genotype have important influences on clinical severity and treatment outcomes. Clinical guidelines emphasize early initiation of ERT before severe deterioration of respiratory function and bone mineralization occur to ensure better prognosis in patients with perinatal or infantile HPP[12]. Considering the high cost of this therapy, collaborative efforts are needed to support treatment decision-making. This is also a challenge for adult patient group. HPP should be considered when serum ALP levels are consistently lower than the normal range in terms of age and sex.

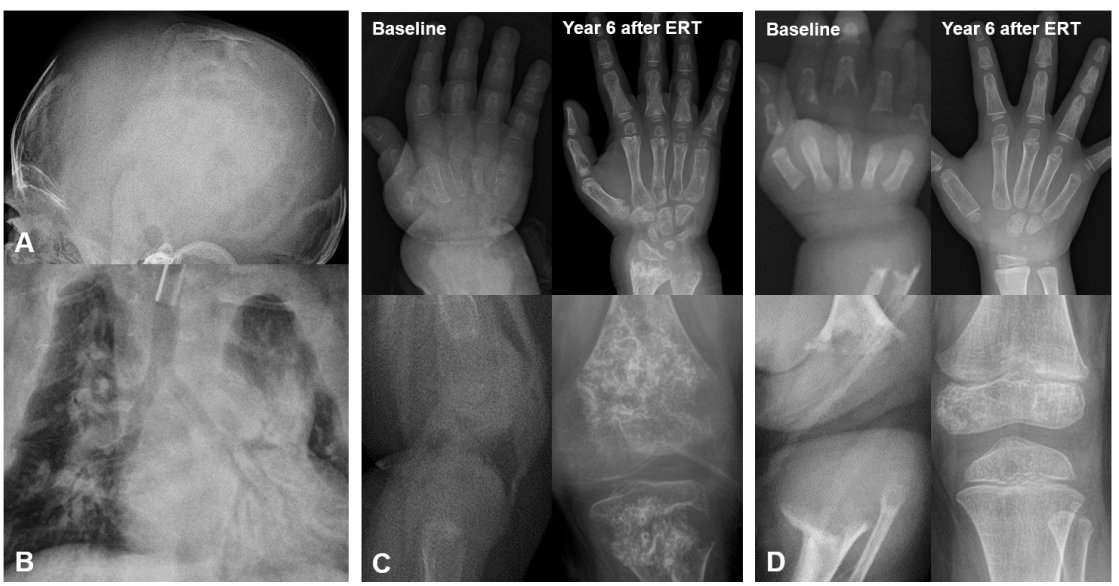

Fig. 1. Radiographic findings of patients with hypophosphatasia (HPP). (A), (B), and baseline images of (C) are of a 21-month-old patient with infantile HPP before starting enzyme replacement therapy (ERT). Severe fontanelle widening, thin ribs, irregular osteolytic bone change with metaphyseal fraying in bones of leg, wrist, and hand can be seen. The images in (D) are baseline images before ERT and images after 6 years of ERT in a patient with perinatal lethal HPP who started ERT at 1 month of age. The patient who started ERT earlier showed better skeletal improvement.

2. Hereditary hypophosphatemic rickets

The most common hereditary hypophosphatemic rickets is the X-linked form (XLH), which occurs due to a mutation in the PHEX gene. The prevalence of XLH is approximately 1 in 20,000[13]. PHEX gene is involved in the downregulation of FGF23, which inhibits the renal production of 1,25-dihydroxyvitamin D3 and reabsorption of phosphate by lowering 1-α-hydroxylase in the renal proximal tubule[14]. The diagnosis of XLH is based on the clinical manifestations, laboratory findings, and radiographic findings. The clinical characteristics include hypophosphatemia, deformity of the lower limb, bone pain, and growth retardation. Dental problems, such as tooth abscesses, can also occur. Radiological signs of XLH in the hands, knees, and lower limbs include long bone deformities (valgus or varus) and abnormal growth plates with widened and frayed metaphyses (Fig. 2).

Biochemical criteria for the diagnosis of XLH include:

- Serum phosphate levels below the normal threshold in terms of age associated with renal phosphate wasting, for example, reduced calculated maximal tubular reabsorption of phosphate as a function of glomerular filtration rate (TmP/GFR)[15].
- ALP levels above the upper limit of normal in terms of age.
- Parathyroid hormone (PTH) levels within the normal or upper normal range
- Normal serum calcium levels and low urinary calcium excretion.

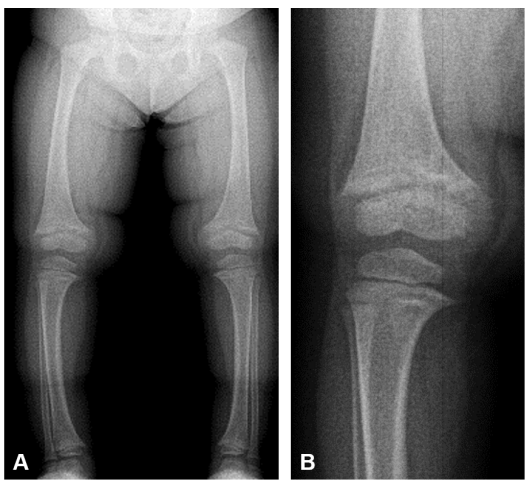

Fig. 2. Radiographic findings of a 39-month-old patient with X-linked hypophosphatemic rickets (XLH). (B) is the image of the right knee of (A). Radiologic findings of genu varum, metaphyseal flaring and decreased bone density are evident.

The final confirmation of XLH is through genetic analysis, which identifies mutations in the PHEX gene in approximately 70% of patients with hypophosphatemic rickets and 85-90% of patients when the disease is familial.

Medical treatment of XLH has included oral phosphate supplementation and active vitamin D analog (alfacalcidol or calcitriol) administration for decades[16]. However, several limitations of this therapy have been identified over the years, including absence of correction for phosphate wasting, and the risk of nephrocalcinosis and hyperparathyroidism. Severe cases require surgery, such as osteotomy or epiphysiodesis[17]. Not all patients tolerate liquid phosphate well; therefore, compliance may be a challenge. A new treatment for XLH involves administration of a recombinant humanized monoclonal IgG1 antibody against FGF23 (Burosumab, Crysvita®, Ultragenyx). Results from phase 2 and 3 studies have shown that Burosumab can reduce the loss of phosphate from the kidneys, improve abnormally low serum phosphate concentrations, and reduce the severity of rickets, as shown by radiologic findings[18]. Burosumab was recently approved by the European Union for treatment of XLH in children above the age of 1 year and adolescents who are still growing. The drug is being used in the United States for treatment of all patients affected by XLH above the age of 1 year. In Korea, this treatment will be used for patients who fit the initial criteria under insurance coverage in the coming time. The limitations of this treatment

include injection site reactions, headaches, muscular pain, and limited gain in growth velocity. Therefore, long-term outcomes should be investigated.

3. Gaucher disease

GD, an autosomal recessive inherited lysosomal storage disorder, is caused by the deficiency of beta-glucocerebrosidase enzyme (GBA), which results in accumulation of glucocerebroside (GC) within tissue macrophages in multiple organs. Storage of GC in macrophages causes hepatosplenomegaly and involvement of the bone marrow. Severe bone marrow infiltration by lipid-laden macrophages can occur in GD. There are three subtypes of GD, types 1, 2, and 3, classified on the basis of presence of neurological deterioration, age at the time of identification, and progression rate[19]. Type 1 GD manifests as splenomegaly, hepatomegaly, anemia, thrombocytopenia, bone disease and growth retardation[20]. Patients with type 2 GD typically exhibit neurodegeneration and hepatosplenomegaly before one year of age. Most type 2 patients die at birth or within 2-3 years of life[21]. Type 3 GD is a chronically progressive form, wherein the onset of neurological symptoms occur at ≥1 year of age.

Clinical or radiographic evidence of bone disease is evident in 70%-100% of individuals with type 1 GD[22]. Bone diseases range from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis[23]. Bone involvement, which can lead to acute or chronic bone pain, pathological fractures, and subchondral joint collapse with secondary degenerative arthritis, is often the most debilitating aspect of type 1 GD[24]. Bone crises usually manifests as acute bone pain confined to one extremity or joint[25], and are often accompanied by fever and leukocytosis with sterile blood culture. Radiography may reveal Erlenmeyer flask deformities in the distal femur and endosteal scalloping caused by bone marrow infiltration (Fig. 3). MRI can be used to estimate the extent of marrow involvement and presence of fibrosis and/or infarction. Osteoporosis frequently occurs in these patients. Bone disease may not correlate with the severity of hematological or visceral problems in patients with GD. Three recombinant glucocerebrosidase enzyme preparations are currently available: imiglucerase (Cerezyme®), velalglucerase alfa (VPRIV®), and imiglucerase (Abcertin®). Regular intravenous infusion of recombinant enzymes (ERT) have been proven to be safe and effective for treating hematologic and visceral involvement. However, the efficacy of ERT has not been reported to be consistent with improvements in neurologic symptoms[26]. Since the tight junctions of the blood-brain barrier block the passage of ERT drugs, improvements in CNS involvement are limited. Early diagnosis and prompt treatment initiation is crucial; however, patients with GD frequently experience significant diagnostic delays that can lead to complications[27]. Timely administration of intravenous ERT or oral substrate inhibitors can prevent skeletal complications. ERT, hematopoietic stem cell transplantation (HSCT), substrate reduction therapy (SRT), and pharmacological chaperone therapy (PCT) are currently

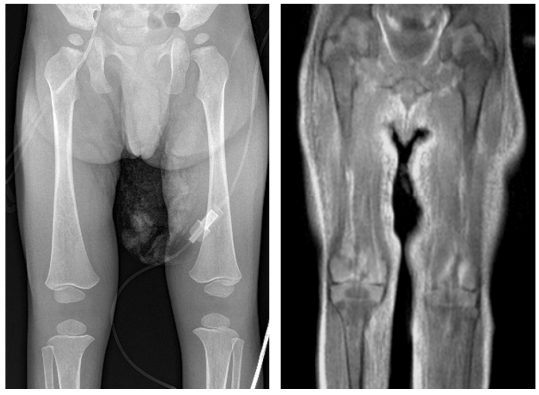

Fig. 3. Radiographic and MRI images of a 19-month-old patient with Gaucher disease. X-ray shows broad diaphysis and metaphyseal flaring of femur (Erlenmeyer flask deformity) as a result of under tubulation. T1-weighted MRI image shows low signal intensity of bone marrow, suggesting diffuse bone marrow involvement of Gaucher cells.

being used to treat patients with GD. Furthermore, the potential of gene and stem cell therapies in treatment of GD are being investigated[22].

4. Mucopolysaccharidoses

Skeletal abnormalities are the hallmark of lysosomal storage disorders, and are caused by accumulation of glycosaminoglycans (GAGs) in MPS. There are 11 types of MPSs, each caused by a deficiency of one of the 11 enzymes[28]. MPSs are multisystemic disorders with various severity and distinct clinical features (Table 3). However, skeletal deformities are universal and usually start at an early age due to the accumulation of GAGs in bone and cartilages. These pathological processes lead to growth retardation due to damage to the cartilage, destruction of the growth plate, and incomplete ossification. Numerous lysosomal storage disorders, particularly the MPSs, are characterized by a combination of radiographic features, dysostosis multiplex. This includes "J"-shaped sella, oar-shaped ribs, anterior inferior beaking of the vertebral bodies, flared iliac wings, dysplastic femoral heads, "bullet-shaped" proximal phalanges, and central pointing of the proximal metacarpals[29] (Fig. 4). These deformities have been associated with abnormal bone remodeling. GAG accumulation has been reported in osteoblasts, osteoclasts, and chondrocytes in animal models of MPS and in a human case report. Therefore, it was hypothesized that GAG accumulation impairs cellular function in bone. In addition, increased levels of inflammatory biomarkers in MPS may also be associated with impaired bone function. The range of motion of multiple joints is reduced to a variable degree in all types of MPS[30], except type IVA, where joint laxity occurs[31]. As patients age, progressive joint damage and secondary arthritic changes lead to greater limitation of mobility. Hip surgery is often performed to ameliorate pain and maintain the walking ability[32]. Skeletal pain is a frequent complaint in MPS patients[33]. Other skeletal problems associated with MPSs include restrictive pulmonary disease caused by altered shape of the thorax, thoracic wall stiffness, and spinal cord compression, which leads to severe neurological symptoms. Definitive diagnosis relies on enzymatic assay and genetic testing. Determining the type of GAG in urine can help distinguish the enzyme that is deficient. However, the diagnosis of MPS is often delayed because the majority of patients appear normal in the early stages. Moreover, their total GAG levels in urine may be normal, thus yielding a

Table 3. Recognition of mucopolysaccharidosis (MPS)

Clinical features	MPS I	MPS II	MPS III	MPS IV	MPS VI	MPS VII
Coarse facial features	+	+	-/+	-/+	+	+
Cognitive retardation	-/+	-/+	+	-	-/+	+
Epilepsy	+	+	+	+	+	-
Hepatosplenomegaly	+	+	+	-/+	+	+
Valve disease	+	+	+	+	+	+
Inguinal and umbilical hernias	+	+	+	+	+	+
Corneal clouding	+	+	+	+	+	+
Short stature	+	+	-/?	+	+	+
Kyphoscoliosis	+	+	+	+	+	+
Joints stiffness	+	+	-/?	-	+	+
Hearing loss	+	+	+	+	+	+
Teeth abnormalites	+	+	+	+	+	+
Enlarged tongue	+	+	+	+	+	+
Hydrops fetalis	-	-	-	-	-	+

false negative result[34]. Therefore, newborn screening and identification of more sensitive biochemical markers are required to diagnose MPS in a timely and precise manner. Conservative treatment and surgery are intended to mitigate symptoms and reduce suffering. At present, disease-specific treatments for MPS include HSCT and ERT. However, the major limitations of HSCT include the rarity of matching donors and transplant rejection. Clinical ERT trials have reported positive results for MPS I, II, IVA, VI, and VII[35-39]. Both HSCT and ERT have proven to be unsatisfactory in patients with MPS III, since MPS III is a special type of MPS that mainly involves the CNS[40]. Adverse effects of ERT have been reported, and anti-ERT antibodies have been observed in most of the patients[41]. Moreover, the efficacy of ERT treatment is reduced by its low level of blood-brain barrier penetration and inefficient delivery to avascular tissues, including bone. Intracerebroventricular ERT is ongoing in Korea to overcome the CNS limitations. Approved therapeutics and ongoing clinical trials are summarized in Table 4.

Treatment

Therapeutic approaches differ due to variations in the pathophysiological mechanisms of inborn errors of metabolism with skeletal involvement. Generally, adequate intake of calcium, phosphate, and vitamin D along with optimal physical activity are recommended. However, achieving optimal physical activity can be challenging in patients with cognitive dysfunction. Skeletal dysplasia, arthropathy, and/or reduced bone mineral density are symptoms of numerous inborn errors of metabolism. For several disorders, disease-specific therapies influencing the bone metabolism are or will become available; for example, asfotase alfa for HPP, anti-IGF23 for hypophosphatemic rickets, and nitisinone for alkaptonuria. The long-term effects of

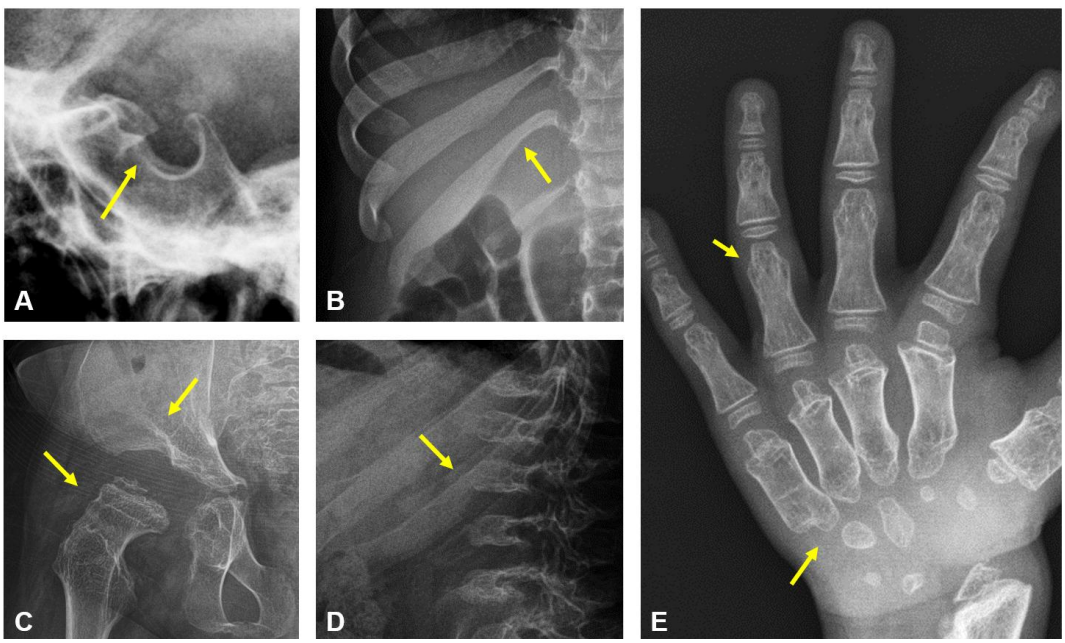

Fig. 4. Dysostosis in mucopolysaccharidoses (MPSs). (A) and (B) are images of a patient with MPS type II. (C, D), and (E) are images of MPS type IV patients [(C) and (D) are images of the same patient]. The following radiographic findings can be identified in each image; (A) J-shaped sell turcica, (B) oar-shaped ribs, (C) beaking of vertebral bodies, (D) flared iliac wings and dysplastic femoral head, (E) bullet-shaped proximal phalanges, central pointing of the proximal metacarpals.

these drugs on skeletal manifestations of these disorders remain to be established. With the development of disease-specific targeted therapies and supportive care, more patients survive into adulthood, and skeletal symptoms have become a more prominent feature of these disorders. This makes awareness of these skeletal symptoms and options for management of the accompanying complaints more important. Pain control, physiotherapy, and well-timed surgical interventions performed by an expert team skilled in treating these complex multisystem disorders remain the cornerstone of disease management. The importance of improving the quality of life of these patients by maintaining mobility should not be underestimated.

Table 4 List of approved therapeutics and clinical trials in MPS

Type	FDA-Approved ERT Therapy	Ongoing Trials	
		ERT-CNS	Combination Therapy/Gene Therapy/ Cell Therapy/Substrate reduction
MPS I	Laronidase	IT-laronidase IV-AGT-181 (Valanafusp alpha, mAb fusion protein)	Laronidase/HSCT Laronidase/immunosuppressive agents HSCT/immunosuppressive agent IV-SB-318 (AAV2/6 vector) IV-RGX-111 (AAV9 vector) ICV-RGX-111 (AAV9 vector) IV-ISP-001 (Human IDUA-producing B cell) IV-SIG-005 (Human IDUA)
MPS II	Idursulfase Idursulfase beta	IT-idursulfase ICV-idursulfase beta IV-AGT-182 (Valanafusp alpha, Ab fusion protein) IV-JR-141 (mAb fusion protein) IV-DNL310 (ETV-IDS, fusion protein)	IT-Idursulfase/IV-Elaprase IV-SB-913 (AAV2/6 vector) IV-RGX-121 (AAV9 vector) IV-EGT-301 (AAV9 vector)
MPS IIIA		IT-HGT-1410 (rh heparin-N-sulfatase) IT-rhSGSH IV-SOBI003 (rhSGSH) IV-AGT-184 (Valanafusp alpha, mAb fusion protein)	IV-ABO-102 (AAV vector) IV-EGT-101 (AAV9 vector) IV-LYS-SAF302 (AAV vector) IV-OTL-201 (Autologous CD34+ cells) ICV-EGT-101 (AAV9 vector) ICV-LYS-SAF302 (AAV vector) IP-SAF301 (AAV vector) IP-LYS-SAF302 (AAV vector)
MPS IIIB		ICV-AX 250 ICV-tralesinidase alfa (rhNAGLU-IGF2) IV-SBC-103 (rhNAGLU) BMN-250 IGF-alpha-N-acetylglucosaminidase fusion	IV-ABO-101 (AAV vector) IV-EGT-201 (AAV9 vector) IP-AAV5-hNAGLU
MPS IVA	Elosulfase alpha		
MPS VI	Galsulfase		HSCT/immunosuppressive agent IV-AAV vector NCT03173521 (systemic) PO-IVA336 (Odiparcil's)
MPS VII	Vestronidase alfa-vjbk		HSCT/immunosuppressive agent

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