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종 설

Inborn Errors of Metabolism with Bony Manifestation

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Introduction

Skeletal dysplasias are a group of disorders of bone and/or cartilage associated with generalized skeletal abnormalities. The overall incidence is estimated to be about 1 in 5000 live births[1]. Currently, there are more than 400 skeletal dysplasias classified by a clinical, radiographic and molecular basis[2]. The genetic pathogenesis of a majority of this group are being proven as inborn errors of metabolism due to single gene defects. Of the many skeletal dysplasias, which we plan to introduce in due order in future reviews, this overview will focus on mucopolysaccharidosis. Mucopolysaccharidosis are a group of lysosomal storage disorders due to inborn errors of metabolism which show typical features of skeletal dysplasia with similarities shared between different subgroups.

Mucopolysaccharidosis

Mucopolysaccharidoses (MPSs) are a group of rare genetic disorders, classified as lysosomal storage diseases (LSDs)[3]. This disease is one of the many skeletal dysplasias. MPSs are characterized by deficiency of lysosomal enzymes responsible for the normal degradation of glycosaminoglycans (GAGs) or mucopolysaccharides[4]. This enzyme deficiency leads to progressive lysosomal accumulation of GAGs and their excretion in the urine, followed by the development of various somatic and neurologic symptoms[3, 5] (Table 1). MPSs are categorized into seven types (I, II, III, IV, VI, VII and IX) based on the affected enzyme[3, 6] (Table 2). Extensive somatic involvement affecting the heart, lungs, bones, joints and gastrointestinal system is seen in most types of MPS, accompanied with central nervous system (CNS) dysfunction in MPS I, II, III and VII[3, 5]. The participation of a multidisciplinary team of specialized professionals is recommended for the diagnosis, treatment, and monitoring of patients with MPS, because these diseases are rare and exhibit multisystemic involvement.

Dysostosis multiplex

Dysostosis multiplex is the term used to describe the constellation of radiographic changes characteristically seen in MPS[7]. These skeletal abnormalities include flattened vertebral bodies (platyspondyly) with anterior beaking, odontoid hypoplasia, thoracolumbar kyphosis, oar-shaped

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Table 1. Signs and Symptoms Suggestive of MPS

Common bone and joint features
Early joint involvement without classic inflammatory features or erosive bone lesions
Claw hand
Spinal deformity (subtle or overt gibbus, scoliosis, kyphosis, lordosis)
Radiological evidence of dysostosis multiplex
this supplement)
Other common clinical signs
Coarsening of facial features over time
Corneal clouding (can be mild or severe)
Short, stiff neck
Frequent respiratory infections, chronic nasal congestion, noisy breathing/snoring
Heart murmur
History of hernia repair surgery (inguinal and/or umbilical)
Short stature
Abnormal gait (especially toe walking)
Abdominal protuberance due to liver and spleen enlargement

Table 2. Classification of MPS

Type of MPS	Storaged GAG	Deficient enzyme	Gene	Genetic locus	Inheritance
MPS I	DS, HS	a-L-iduronidase	IDUA	4p16.3	AR
MPS II	DS, HS	Iduronate-2-sulphatase	IDS	Xq28	XR
MPS IIIA	HS	heparan N-sulphatase	SGSH	17q25.3	AR
MPS IIIB	HS	a-N-acetylglucosaminidase	NAGLU	17q21	AR
MPS IIIC	HS	acetyl-CoA: a-glucosaminideacetyltransferase	HGSNAT	8p11.1	AR
MPS IIID	HS	N-acetylglucosamine 6-sulphatase	GNS	12q14	AR
MPS IVA	KS, CS	galactose 6-sulphatase	GALNS	16q24.3	AR
MPS IVB	KS	b-galactosidase	GLB1	3p21.33	AR
MPS VI	DS, CS	Arylsulphatase B	ARSB	5q11-q13	AR
MPS VII	DS, HS, CS	b-Glucuronidase	GUSB	7q21.11	AR

Abbreviations: MPS I, Hurler, Hurler_Scheie, Scheie syndromes; MPS II, Hunter syndrome; MPS III A-D, Sanfilippo syndrome; MPS IV A, B, Morquio syndrome; MPS VI, Maroteaux-Lamy syndrome; MPS VII, Sly syndrome

ribs, short thickened clavicles, bullet-shaped phalanges (short and thick with proximal widening), a large skull with a thickened calvarium and J-shaped sellaturcica. Changes in the lower extremities include dysplastic femoral heads, flattened acetabula, hypoplasia of the inferior portions of the iliac bones with flared iliac wings, coxavalga and genu valgum deformities (Table 3).

MPS type I

MPS I is caused by a lack of a-L-iduronidase (IDUA) required for the breakdown of GAGs, mainly heparansulphate and dermatansulphate. MPS I, like the majority of lysosomal diseases, is inherited in an autosomal recessive manner and has an incidence of approximately 1 in 100,000 live births for the Hurler phenotype and up to 1 in 800,000

Table 3. Major Musculoskeletal Manifestations of MPSs

Disorder	Musculoskeletal manifestations
MPS I (Hurler)	Dysostosis multiplex, disproportionate short stature, joint contractures, CTS, odontoid hypoplasia, atlanto–axial instability, acetabular dysplasia, coxavalga, genu valgum, trigger digits
MPS I (H–S, Schiei)	Milder manifestations of Hurler syndrome
MPS II/Hunter	Dysostosis multiplex, disproportionate short stature, joint contractures, CTS, odontoid hypoplasia, atlanto–axial instability, acetabular dysplasia, coxavalga, genu valgum, trigger digits
MPS III	Mild somatic manifestations only, mild short stature and contractures in a small proportion (mainly elbow joint)
MPS IV	Severe skeletal dysplasia, dysostosis multiplex, disproportionate short stature, joint hypermobility, odontoid hypoplasia, atlanto–axial instability, acetabular dysplasia, hip dislocations, coxavalga, genu valgum, pesplanus, pectuscarinatum
MPS VI	Dysostosis multiplex, disproportionate short stature, joint contractures, CTS, odontoid hypoplasia, atlanto–axial instability, acetabular dysplasia, coxavalga, genu valgum, trigger digits, pectuscarinatum
MPS VII	Dysostosis multiplex, disproportionate short stature, joint contractures, odontoid hypoplasia, atlanto–axial instability, acetabular dysplasia, pectuscarinatum

live births for the Scheie phenotype. The most common manifestations of MPS I include characteristicfacies, corneal clouding, macroglossia, hearing loss, hydrocephaly, cardiopathy, respiratory problems, hepatosplenomegaly, inguinal and umbilical hernia, dysostosismultiplex, limited joint mobility, and cognitive impairment[8]. In addition, the accumulation of GAGs in rigid structures and paraspinal ligaments increases the potential for morbidity, resulting in major risks to the cervical column. Due to the involvement of various organs and tissues, patients with MPS I frequently require surgical interventions with a high rate of complications[9].

MPS I is further divided into three clinical subtypes: Hurler syndrome (MPS IH, severe), Hurler–Scheie syndrome (MPS IH/S, intermediate) and Scheie syndrome (MPS IS, attenuated; formerly known as MPS V). In each phenotype, considerable heterogeneity and overlap can be found with espect to the symptoms and their severity.

Severe form (Hurler syndrome): This is the most severe MPS I phenotype, characterized by impaired cognitive development, progressive coarsening of facial features, hepatosplenomegaly, respiratory failure, cardiac valvulopathy, recurrent otitis media, corneal clouding, musculoskeletal manifestations such as joint stiffness and contractures, and dysostosis multiplex. The symptoms arise after birth and progress rapidly. Most of the patients with the severe phenotype which are not submitted to a specific treatment progress to death, on average, before the age of 10 years, due to complications related to brain damage or cardiorespiratory problems.

Attenuated form (Hurler–Scheie syndrome): This phenotype manifests in infancy, however with intermediate severity when compared with the Hurler phenotype. The somatic symptoms reduce life expectancy to the second or third decade of life. Generally, there is no cognitive impairment, but some patients may exhibit mild learning difficulties.

Scheie syndrome: This is the most attenuated

form of MPS I, in which the symptoms occur later and progress slowly. Patients exhibit normal intelligence and survive until adulthood.

MPS type II

Unlike all the other MPSs that show autosomal recessive inheritance, MPS II (Hunter syndrome) is an X-linked condition. Therefore, it affects males almost exclusively, although a few female cases have been reported. MPS II is caused by a lack of iduronate-2-sulphatase (I2S), leading to the accumulation of heparansulphate and dermatansulphate within the lysosome[10]. Hunter syndrome is the most common subtype in Asia, including Korea. MPS II is a chronic, progressive disease with a clinical picture similar in certain aspects to that of MPS I: there is great variability in the clinical manifestations, including central nervous system involvement, and can therefore be classified into a severe or "neuropathic" form and an attenuated or "non-neuropathic" form. In its most severe form somatic involvement becomes evident in the first years of life. At birth the affected boys appear normal although they tend to be heavy and to have an increased head circumference[9]. Further symptoms in early childhood include inguinal and umbilical hernia, hepatosplenomegaly and coarse facial features. A gibbus may be seen even before the second year of life. Later on, mobility becomes more restricted due to joint contractures that are caused by both metaphyseal deformities and thickened joint capsules. Recurrent upper and lower respiratory infections are a very common symptom. A skin abnormality, namely pebbly, ivory-coloured lesions over the back, upper arms and lateral aspects of the thigh are unique to Hunter syndrome. Their presence, however, does not correlate with the clinical severity. The skeletal disorder, generally known as dysostosis multiplex, results in disproportionate dwarfism characterized by short trunk and chest deformities. As an initial sign of cerebral involvement a delay in developmental milestones such as the ability to walk or to speak is observed. Mental impairment is progressive, leading to rapid deterioration of social and adaptive skills[10]. Patients lose contact with the environment as a result of progressive dementia. Common causes of death that usually occur within the second decade of life are obstructive airway disease, cardiac failure, choking and infections. In patients with the attenuated (so-called adult) form, major clinical manifestations are joint contractures, obstructive and restrictive airway disease, cardiac disease and skeletal deformities. These patients have a normal intelligence, but often have many complaints such as progressive loss of vision due to retinal dysfunction, spastic paresis due to myeloid compression at the cranio-cervical region, severe hip disease and cardiac complications. Less well known complications include the gastrointestinal complications in Hunter patients, which present as short periods of watery diarrhea that may occur without obvious cause and which are difficult to manage[10].

MPS type III

MPS III, or Sanfilippo Syndrome, is an autosomal recessive disorder characterized by the absence of 1 of 4 enzymes essential in the metabolism of heparan sulfate: heparan N-sulfatase, a-N-acetylglucosaminidase, acetyl-coenzyme A a-glucosaminide-N-acetyltransferase, and N-acetylglucosamine-6-sulfatase[6]. 2 The lack of each of these enzymes creates 4 subcategories

of MPS III, known as types A, B, C, and D, respectively. The incidence of MPS III (all 4 types combined) is estimated to be 1 in 70,000 births. Phenotypically, these types are essentially indistinguishable. The most pronounced symptom in MPS III is severe deterioration of the central nervous system. This is manifested in the form of aggression and sleep disturbances. Visual changes, difficulty in breathing and swallowing, respiratory infections, heart disease, enlarged liver and spleen, and hernias are also present. The average life expectancy of a patient with MPS III is from late teens to early twenties.

The effects of MPS III on the musculoskeletal system are less severe than those caused by other forms of MPS[11]. MPS III subtypes are difficult to distinguish clinically; however, MPS IIIA tends to lie on the most severe end of the spectrum. Patients often fall into a semi-vegetative state and usually survive until the second or third decade of life[3].

MPS type IV

MPS IV (Morquio syndrome) exists in two forms, MPS IVA and MPS IVB, caused by the absence of N-acetylgalactosamine-6-sulphate sulphatase (GALNS) and b-galactosidase (GLB1), respectively. These enzymes are involved in the catabolism of keratansulphate and chondroitin sulphate that are largely distributed in the cornea, bone and cartilage. Therefore, MPS IV is characterized by a wide array of musculoskeletal symptoms such as pectuscarinatum, scoliosis, kyphosis and genu valgum[7]. The incidence of MPS IVA in the general population is estimated to be 1: 201,000[12]. In patients with MPS IVA, KS and C6S accumulation typically results in short stature and skeletal dysplasia. Bone deformity is the most common initial manifestation of skeletal dysplasia. Additional compromised systems include the visual system, auditory system, cardiovascular system, and respiratory system. The central nervous system is not believed to have significant manifestations of GAG accumulation and normal intelligence appears to be preserved. However, patients have a high risk of developing neurological complications caused by a combination of odontoid hypoplasia, incomplete ossification of the anterior and posterior rings of the atlas, and deposition of GAGs in the anterior extradural space. This results in atlantoaxial subluxation and spinal cord compression, with cervical myelopathy, consequential quadriparesis or even death.

There is a wide spectrum of disease progression among individuals with MPS IVA[13]. A high degree of genetic heterogeneity is likely responsible for this phenotypic variety. More than 180 different mutations have been identified in the GALNS gene. Onset of disease symptoms commonly occurs prior to 1 year of age in severely affected (rapidly progressing) patients or as late as the second decade of life in less severely affected (mild) patients. Especially MPS IVA may often be radiographically confused with other skeletal dysplasias/entities, in particular MED, SED, and bilateral Perthes-like disease. Therefore, combined radiographic, clinical, biochemical and molecular findings are important to achieve an accurate diagnosis.

MPS type VI

In MPS VI (Maroteaux-Lamy syndrome), the absence of N-acetylgalactosamine 4-sulphatase (arylsulphatase B; ASB) leads to accumulation of

dermatansulphate and chondroitin sulphate. The estimated incidence of MPS VI is 0.23 per 100,000 live births but in Brazil preliminary data Guidelines for the treatment of MPS indicate that this incidence is higher[9].

The clinical presentation of MPS VI varies greatly with age of onset and rate of disease progression[14]. Compared to the rapidly progressing disease where severe symptoms occur in several systems simultaneously, the slowly progressing disease may have clinically significant symptoms occurring in fewer systems. Patients with MPS VI exhibit a wide variability of multisystemic symptoms with a chronic and progressive course, where primarily the skeletal and cardiopulmonary systems, cornea, skin, liver, spleen, brain, and meninges are affected. The somatic involvement can resemble that of individuals with MPS I, but the patients' intelligence are usually normal. In general, patients have a short trunk and a thoracolumbar gibbus. Ocular manifestations include corneal clouding, glaucoma, pseudoglaucoma, and papilledema with optic atrophy in more advanced stages. Hypoacusia is the most common otological manifestation, generally associated with a conductive and neurosensory component. Respiratory involvement results from extrinsic and intrinsic alterations to the airways. A short neck, elevated epiglottis, deep cervical fossa, hypoplastic mandible, and tracheobronchomalacia contribute to the respiratory problems. Obstructive sleep apnea is also a frequent complication in MPS VI[14].

Although patients with MPS VI do not exhibit mental retardation as a direct consequence of the disease, their cognitive acquisitions may be impaired by the auditory and visual deficits and by the physical limitations inherent to the disease. Physical growth and development may be normal in the first years of life, stagnating at around six or eight years of age. Cardiac involvement is a significant component of this disease and is responsible for a large part of the patients' morbidity and mortality. Most of the individuals with MPS VI progress to death in their 2nd or 3rd decade of life, with heart failure, often secondary to chronic respiratory obstruction, as the primary cause[15].

Diagnosis of MPS

The measurement of urinary GAG levels is a useful screening test for the MPS disorders. A positive result is very suggestive of an MPS, but false-negative results are very common[16]. False negative results occur because of a lack of sufficient sensitivity in the various assays and because of samples that are too dilute. Thus a negative urinary GAG analysis does not rule out MPS. Therefore, if any patient is clinically suspected of having MPS, but shows a negative urine test, we usually repeat urine GAG. Enzyme activity assays performed on cultured fibroblasts, leucocytes, plasma or serum are definitive for a specific MPS disorder and are considered the gold standard for diagnosis[6]. Because gene sequencing follows biochemical diagnosis in order to identify the mutation(s) present in almost all patients in Korea, we usually do not measure the activity of another sulphatase in order to rule out multiple sulphatase deficiencies when a sulphatase deficiency is identified. However, if the result of gene sequencing is not definite to confirm the disease, measurement of the activity of another sulphatase should be done.

Korean patients with MPS

Based on the data from Samsung Medical Center, which has been the main center for diagnosis and treatment for patients with MPS in Korea, there have been 147 patients with MPS confirmed by enzyme assay and molecular analysis from 1994 to 2013. The most common subtype of MPS was Hunter syndrome (54.6%), and the second most common subtype was MPS type III (18.4%). Other subtypes comprised 15.3% (MPS type I), 9.5% (MPS type IV), 1.4% (MPS type VI), and MPS type VII has not been found until now. ERT has been available for patients with MPS type I, VI, and II since 2004, 2008, and 2009, respectively.

Enzyme replacement therapy of MPS

The management of patients with MPS requires regular assessment, supportive care and a multidisciplinary clinical team that can address a variety of systemic complications. The burden of surgery is often very high for MPS patients with severe somatic involvement. Due to the complexity and rarity of these disorders, patients are best monitored and treated at a facility that has experience treating patients with MPS. In this regard, it is important to note that MPS patients with airway involvement and/or atlanto-axial instability who need to undergo a procedure requiring anesthesia have a particularly high risk of complications.

Early and accurate diagnosis of the MPS disorders is imperative to optimize treatment outcomes, particularly for those disorders that are amenable to treatment with HSCT or ERT.

The treatment of MPS was palliative prior to the introduction of enzyme replacement therapy (ERT). For over about 10 years, ERT with recombinant human enzyme for MPS I, II and VI has been approved in the USA, Europe, Korea, and many other countries worldwide[15, 17–19] (Table 4). Intravenously infused enzymes are internalized via M6P receptors located on the cell surface to reach their target site in the lysosomes and thus replace the defective enzymes. The earlier ERT is initiated, the better the potential outcome because of the irreversible nature of some of the abnormalities associated with the MPS disorders. The certain benefits of ERT for MPS disorders may include improvements in joint mobility, walking ability, and pulmonary and respiratory function; reduction in liver and spleen volume; and significant reduction in urinary GAG excretion[17–20]. ERT administered intravenously does not cross the blood brain barrier at the labeled dose and has not shown benefit for neurocognition[17]. A clinical trial for a drug targeting MPS IVA is underway.

Table 4. Classification of LSD Currently Treated by ERT

	MPS I	MPS II	MPS VI
Drug	Aldurazyme®	Elaprase®/Hunterase®	Naglazyme®
Manufacturer	Genzyme Corp.	Shire HGT/Green cross corp.	BioMarin Pharmaceuticals
Standard dose	0.58 mg/kg	0.50 mg/kg	1 mg/kg
route of administration	intravenously	intravenously	intravenously
Frequency	Weekly	Weekly	Weekly
Infusion time	Approximately 3–4 h	Approximately 3–4 h	Approximately 3–4 h

Unmet needs and Looking forward

The MPS disorders are progressive, life-threatening diseases with a tremendous impact upon quality of life for both patients and their caregivers. While neither HSCT nor ERT represents a cure, it is clear that the key to altering the natural history of the MPS disorders is early and accurate diagnosis and the development of successful therapeutic interventions are aimed at preventing or halting cognitive and somatic deterioration[21]. Many efforts are under way to achieve these goals. Based on the positive somatic data seen with currently available ERT, there has been a push to develop ERT for the use in other types of MPS.

Several approaches for improving delivery of the exogenous enzyme across the tight junctions of the brain parenchyma are under investigation: such as high dose systemic ERT[22], direct intrathecal administration of ERT[23], gene therapy[24], and receptor-mediated enzyme replacement therapy of the brain (Trojan horse).

1. High dose systemic ERT

Several approaches for improving delivery of the exogenous enzyme across the tight junctions of the brain parenchyma are under investigation. Variable outcomes have been observed with high-dose ERT, from reduced neuropathology in MPS II and VII mice to no effect in MPS IIIA mice. To date, the only treatment available is systemic infusion of IDS, which ameliorates certain exclusive visceral defects. Therefore, it is important to simultaneously treat the visceral and CNS defects of MPS II patients. We investigated whether early initiated, high-dose ERT decreased GAG in the brain of IdS-knockout mice[22]. High-dose systemic ERT started early in life could be a promising therapeutic modality for improving neurologic dysfunction in children with severe Hunter syndrome.

2. Direct intrathecal administrations

Direct intracerebral and intrathecal administrations have been tested with some success in clearing GAG storage in the brain and delaying neurodegeneration in animals with MPS I, II, III and VI. Intermittent intrathecal (IT) injection of the enzyme has been introduced as a method to overcome the blood-brain barrier, and we investigated responses in the brain of MPS II mice with varying doses of continuous IT infusion of recombinant human IDS (rh-IDS) by using an osmotic pump in three different doses (2.4, 4.8, and 12 mg/day) for 3 weeks. Continuous IT infusion of the deficient enzyme was thought to be more physiologic, and was effective in improving CNS defects in the MPS II mice[23]. This could be a valuable therapeutic method for treating neurological deterioration in patients with MPS II. We suggest an application of weekly intravenous ERT combined with monthly intrathecal therapy for patients with MPS in the future.

3. Gene therapy

In recent years, gene therapy has attracted much attention as it has the potential to provide a stable source of the enzyme with effective delivery to both the brain and skeletal structures. In vivo gene therapy refers to inserting a wild copy of the defective gene into a recombinant

vector, which is then administered systemically or localized to a depot site such as the liver or muscle for expression. In turn, the functional enzyme is expressed in the organs where it is needed, enabling the widespread correction of the lysosomal pathology. We generated an IDS knockout mice, a mouse model of human MPS II, and evaluated the effect of gene therapy with a pseudotyped, recombinant adeno-associated virus 2/8 vector encoding the human IDS gene (rAAV-hIDS) in IDS-deficient mice[24]. IDS activity and GAG levels were measured in serum and tissues after therapy. Gene therapy completely restored IDS activity in plasma and tissue of the knockout mice. The rescued enzymatic activity completely cleared the accumulated GAGs in all the tissues analyzed. Considering the limitations of the current treatments, gene therapy has arisen as a promising alternative approach. Gene therapy for the MPS disorders has shown good pre-clinical results using different approaches. Viral vectors, especially AAVs or LVs, have shown the best transduction results, and it is reasonable to think that a relatively simple procedure such as systemic gene therapy could be used to treat these disorders.

Future in the MPS treatment

The MPS disorders are progressive, life-threatening diseases with a tremendous impact upon quality of life for both patients and their caregivers. While neither HSCT nor ERT represents a cure, it is clear that the key to altering the natural history of the MPS disorders is early and accurate diagnosis and development of successful therapeutic interventions aimed at preventing or halting cognitive and somatic deterioration. Many efforts are under way to achieve these goals. Based on the positive somatic data seen with currently available ERT, there has been a push to develop ERT for use in MPS IV and VII as well as to investigate the use of intrathecal ERT in order to treat spinal cord compression and to prevent neurological decline[23]. Besides effects of ERT on the brain and bone, more convenient treatment for patients with MPS are unmet needs.

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