Review

DOI: 10.5582/irdr.2014.01013

An overview of Korean patients with mucopolysaccharidosis and collaboration through the Asia Pacific MPS Network

Sung Yoon Cho[1], Young Bae Sohn[2], Dong-Kyu Jin[1,*]

[1] *Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;*
[2] *Department of Medical Genetics, Ajou University Hospital, Ajou University School of Medicine, Suwon, Republic of Korea.*

Summary **Mucopolysaccharidosis (MPS) is a constellation of disorders characterized by the accumulation of mucopolysaccharides in tissues and organs. This accumulation results in the deterioration and degeneration of multiple organs. This paper describes the general distribution of types of MPS in patients, their clinical characteristics and genotypes, the development of animal studies and preclinical studies, enzyme replacement therapy in South Korea, and the development of idursulfase beta and clinical trials on idursulfase beta in South Korea. In addition, this paper discusses academic collaboration among specialists in MPS care in the Asia-Pacific region, which includes Japan, Taiwan, Malaysia, and South Korea, through an organization called the Asia-Pacific MPS Network (APMN). The Asia-Pacific MPS Registry, an electronic remote data entry system, has been developed by key doctors in the APMN. Rare diseases require international cooperation and collaboration to elucidate their mechanisms and carry out clinical trials; therefore, an organization such as the APMN is required. Furthermore, international collaboration among Asian countries and countries around the world will be of utmost importance in the future.**

Keywords: Mucopolysaccharidosis, Hunter syndrome, enzyme replacement therapy

1. Introduction

Mucopolysaccharidosis (MPS) is a constellation of disorders characterized by the accumulation of mucopolysaccharide in tissues and organs. This accumulation results in the deterioration and degeneration of multiple organs. Research has proven that MPS is caused by genetic defects, and at least 11 genes are causally related to MPS disorders. MPSs are categorized into seven types (I, II, III, IV, VI, VII, and IX) based on which enzyme is affected. These types vary in their prevalence, clinical manifestations, and degree of severity. MPS is inherited in an autosomal recessive manner except for MPS type II (Hunter syndrome), which is transmitted as an X-linked recessive disorder (*1*). Extensive somatic involvement affecting the heart, lungs, bones, joints, and gastrointestinal system is seen in most MPS types, accompanied by central nervous system (CNS) dysfunction in MPS types I, II, III, and VII.

Described here are the general distribution of types of MPS in patients, their clinical characteristics, the development of animal studies, and the clinical trials of enzyme replacement therapy (ERT) in South Korea. Also described is academic collaboration among specialists in MPS care in the Asia-Pacific region, which includes Japan, Taiwan, Malaysia, and South Korea, *via* an organization called the Asia Pacific MPS Network (APMN). *Via* the APMN, doctors and researchers who are interested in the treatment of patients with MPS collaborate and exchange information and they present basic and clinical research related to MPS.

2. Distribution of clinical types and genotypes

Although MPS disorders are distributed worldwide, there are regional differences in their distribution. Almost half of the patients in South Korea with MPS have MPS type II, Hunter syndrome, and the same

**Address correspondence to:*
Dr. Dong-Kyu Jin, Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul, 135-710, Republic of Korea.
E-mail: jindk@skku.edu

is true for other locations in Asia such as Japan and Taiwan. In contrast, the incidence of MPS type I is higher than that of MPS type II in Western countries (*2*). The distribution of each type is comparable in South Korea and Japan. However, a point of note is that the prevalence of MPS type III may have been underestimated because therapeutic modalities are not available for this type.

The genotype of each type of MPS in South Korea has been reported several times. Because Hunter syndrome is an X-linked recessive disorder, in most cases the mutations causing the disorder are unique mutations, except when there is a shared X chromosome. The current authors reported finding 20 mutations in 25 Korean patients with MPS type II in 2003 (*3*). Thirty-one mutations in 49 Korean patients with MPS type II from 45 families were later reported in 2012 (*4*). IDS-IDS2 recombination mutations were observed most frequently, and all of the patients with this mutation had the severe phenotype. However, most patients (5/7) with the G374G splicing mutation had an attenuated phenotype, except for two siblings with the severe phenotype. Each patient had a unique individual mutation except for a few recurrent mutations, such as G374G, R443X, and L522P, and recombination mutations.

With MPS type I, several mutations are common to both Asian and Western countries. The current authors reported finding 15 mutations from 10 patients with MPS type I in 2004 (*5*). Later, eight more patients with MPS type I were identified. L346R and 704ins5 accounted for approximately one-third of the mutations found in Korean patients with MPS type I. L346R was mostly found in patients with Hurler syndrome.

The current authors reported a total of seven different mutations in six Korean patients with MPS type IVA in 2013 (*6*). Interestingly, the authors identified three patients with MPS type IVA last year. MPS type IVA is relatively rare in South Korea; thus, extensive screening of orthopedic patients for glycosaminoglycans (GAG) in urine may have contributed to the discovery of this type of MPS. Two mutations, c.451C>A and c.1000C>T, accounted for 33% and 19%, respectively, of all mutations in 13 Korean patients with MPS type IVA. A point worth mentioning is that one patient with an unusual presentation was found through next-generation sequencing (*7*). He first presented with hip pain at 11 years of age, and bilateral Perthes-like disease was suspected. Aggravated hip pain led him to see an orthopedic surgeon at age 27. He is of average stature for an adult Korean male, with a height of 169 cm and a weight of 74 kg. Radiographic abnormalities in the spine, pelvis/hips, and knees led to suspected X-linked spondyloepiphyseal dysplasia (SED) tarda, but this was not confirmed by mutation analysis of SEDL (TRAPPC2). Moreover, molecular testing for SEDC (COL2A1) and multiple epiphyseal dysplasia (COMP, MATN3, and COL9A1-3) revealed no deleterious mutations. Whole-exome sequencing identified two novel GALNS mutations, c.317A>G (p.N106S) and c.553delG (p.E185Rfx14), that were confirmed by Sanger sequencing, and reduced GALNS activity confirmed a diagnosis of MPS type IVA. MPS disease may often be radiographically mistaken for multiple epiphyseal dysplasia, SED, or bilateral Perthes-like disease. A full skeletal survey should be performed if MPS or another type of skeletal dysplasia is suspected. Extra-skeletal manifestations, including corneal clouding, specific cardiac abnormalities, and facial dysmorphology, can provide vital clues.

Mutations in the *GLB1* gene, which encodes acid β-galactosidase, can result in two disease phenotypes, namely GM1-gangliosidosis and MPS type IVB disease. The current authors reported the first known case of Morquio B disease in a Korean patient (*8*). This patient had severe skeletal manifestations (dysostosis multiplex) without CNS involvement. The enzyme activity of β-galactosidase in leukocytes was 1.15 nmol/h/mg protein (reference range 78.1-117.7; 1-1.5% of normal). The patient had compound heterozygous mutations of the GLB1 gene, namely c.13_14insA (p.L5HfsX29), as were reported in a patient with infantile GM1 gangliosidosis. The patient also had near-complete absence of enzyme activity and c.367G>A (p.G123R), which is a novel frame-shift mutation.

3. The clinical profiles of MPS patients in South Korea

In 2012, the current authors retrospectively reviewed the medical records of 75 Korean patients with Hunter syndrome (74 males, one female) in order to investigate the frequency of organ involvement and survival at a single center (*9*). The three most common symptoms of organ involvement were hepatosplenomegaly (99%), facial dysmorphism (97%), and frequent otitis media (91%). Cardiovascular involvement was also common, including valvular abnormalities (89%), left ventricular hypertrophy (68%), and hypertension (30%). The 19 patients who died had a median age of 16.8 years at their time of death. Four of them died within one year of the start of ERT; an autopsy revealed myocardial infarction with severe coronary artery disease in one patient. Two other patients died due to pneumonia and sleep apnea, and the cause of death was not investigated in the remaining case. The high incidence of hypertension and the presence of valvular heart disease indicates that close cardiac monitoring is mandatory in all patients with Hunter syndrome, and especially relatively older patients, even if they are being treated with ERT. A point worth mentioning is the high prevalence, even at a young age, of carpal tunnel syndrome in the patients with Hunter syndrome that were studied. This finding should be considered an integral part of the clinical manifestation

of Hunter syndrome (*10*). Short stature is a prominent and consistent feature in MPS type II. The effect of ERT on the growth of 32 Korean patients with Hunter syndrome was evaluated at a single center (*11*); the patients had marked retardation of growth as they grew older. However, ERT may have less of an effect on the growth of patients with the severe form of Hunter syndrome. The height z-scores in patients over six years of age revealed significant differences. Their growth in response to ERT could be an important treatment outcome or endpoint for future study.

The current authors encountered an interesting case of Hunter syndrome in a female patient, a detailed description of which has been given previously (*12*). The patient had mild manifestations of Hunter syndrome and gave birth to a daughter. Both the mother and daughter carried the p.R443X mutation in the *IDS* gene, and Iduronate-2-sulfatase activity in the mother's fibroblasts was as low as that found in male patients with Hunter syndrome, but it was in the low–normal range in the daughter. Unlike her mother, the daughter did not exhibit any physical signs of Hunter syndrome, and her urinary excretion of glycosaminoglycans was within the normal range. However, she had severe pulmonary vein stenosis with pulmonary hypertension and a large atrial septal defect, and she died at 11 months of age. After several years, the patient subsequently gave birth to a healthy daughter who was not a carrier.

The current authors reported the clinical findings, radiological features, and genetic data from 10 Korean patients with MPS type IVA in 2012 (*13*). Together with three other patients who were diagnosed more recently, Eleven patients had the severe clinical phenotype based on their clinical phenotype criteria, one had an intermediate phenotype, and one had an attenuated phenotype. Radiological findings indicated skeletal abnormalities in all patients, and especially in the hips and extremities. Nine patients had odontoid hypoplasia, and one had mild atlantoaxial subluxation and cord myelopathy. Adequate evaluation and therapy in the early stages may improve the quality of life of patients suffering from skeletal abnormalities and it may reduce the life-threatening effects of atlantoaxial subluxation.

4. Diagnosis of MPS in South Korea

The measurement of urinary GAG levels is a useful test to screen for MPS disorders. A positive result is highly suggestive of MPS, but false-negative results are also very common (*14*). False-negative results occur because of the insufficient sensitivity of the various assays or because the samples are too diluted. Thus, a negative urinary GAG analysis does not rule out MPS. Therefore, the urinary GAG test is usually repeated for any patient who is clinically suspected of having MPS but whose urine test is negative. If the urine GAG level is equivocal in spite of the strong suspicion of MPS, exome sequencing is performed to screen for the several genes that are known to be responsible for MPS.

Enzyme activity assays based on cultured fibroblasts, leucocytes, plasma, or serum are definitive for specific MPS disorders and are considered the gold standard for diagnosis. Because gene sequencing follows biochemical diagnosis to identify the mutation(s) present in almost all patients in South Korea, when a sulfatase deficiency is identified the activity of another sulfatase is not usually measured in order to rule out multiple sulfatase deficiencies. If, however, the results of gene sequencing do not definitively confirm the disease, then the activity of another sulfatase should be measured.

The Samsung Medical Center is the main center for diagnosis and treatment of patients with MPS in South Korea. Based on data from the Center, 147 patients had MPS confirmed *via* enzyme assay and molecular analysis from 1994 to 2013. The most common subtype of MPS was Hunter syndrome (54.6%), followed by MPS type III (18.4%). Thirteen patients with MPS type IIIA were noted, thirteen patients with MPS type IIIB were noted, and one patient with MPS type IIIC was noted. No patients with MPS type IIID were noted. Other subtypes included MPS type I (15.3%), MPS type IV (9.5%), and MPS type VI (1.4%), but MPS type VII has yet to be noted.

5. An animal model of MPS

In 2010, the current authors reported producing IDS knock-out (KO) mice and they analyzed the resulting phenotype (*15*). The KO mouse model of Hunter syndrome was produced by replacing part of the IDS gene (1485 bp encompassing exon 2 and exon 3) with the neomycin resistance gene. This animal model contributed both to basic research and to the development of a novel therapeutic approach.

The auditory characteristics of MPS type II and the effect of ERT on hearing were evaluated in IDS-KO mice. At 17 weeks of age, the IDS-KO mice had elevated hearing thresholds, and exudates were found in the middle ear. The hearing thresholds of the IDS-KO mice treated with enzyme (IDS-ERT) were similar to those of wild type (WT) mice at 17 weeks. Hearing deficits in the MPS type II mouse model can be prevented if ERT is started before the onset of hearing impairment (*16*). The changes in myocardial function associated with ERT were evaluated in a mouse model of cardiomyopathy associated with Hunter syndrome (*17*). Thirty nine-week-old IDS-KO mice received either an intravenous injection of human recombinant IDS (ERT group, $N = 15$) or saline (control group, $N = 15$) for five weeks. A significant increase in left ventricular fractional shortening and radial and circumferential strain was observed in only the ERT group. Marked

myocardial fibrosis was observed only in the control group. In the murine model of Hunter syndrome, ERT has a beneficial effect on cardiac function, and this can be evaluated *via* serial echocardiographic evaluation that includes two-dimensional strain analysis.

Current ERT to treat MPS does not ameliorate the CNS or the skeletal system because the current dose of recombinant enzyme administered is not thought to be able to pass the blood-brain barrier. Several studies on overcoming this barrier were conducted using the KO mouse model of Hunter syndrome.

A pseudotyped, recombinant adeno-associated virus 2/8 vector encoding the human IDS gene (rAAV-hIDS) was administered intravenously to adult IDS-KO mice to evaluate the effects of gene therapy in a mouse model of MPS type II (*15*). Gene therapy completely restored IDS activity in the plasma and tissue of the KO mice, and the restored enzymatic activity completely cleared the accumulated GAGs in all of the tissues analyzed. This experiment involving liver-specific gene therapy indicated the effectiveness of high-dose therapy because the high level of enzyme expression in the liver induced a high level of enzymes in the blood.

Early, high-dose ERT was subsequently found to attenuate ventriculomegaly and histologic abnormalities in the brains of IDS-KO mice (*18*). IDS-KO mice received saline or recombinant human IDS (0.5/1.0/2.0 mg/kg) intravenously once a week, starting at four weeks of age, and continued to do so for 20 weeks. ERT with 2.0 mg/kg, but not 0.5 or 1.0 mg/kg, significantly attenuated the enlarged ventricles, as confirmed by *in vivo* 7.0 Tesla brain magnetic resonance imaging (MRI) at 20 weeks. GAG levels were significantly correlated with the ratio (in percent) of the ventricular volume to the total brain volume. These results suggest that high-dose systemic ERT beginning early in life could be a promising therapeutic modality for improving neurological dysfunction, including ventriculomegaly, in children with severe Hunter syndrome. High-dose enzyme treatment attenuated the ventriculomegaly in this animal model and suggested that the adequate therapeutic range for this disorder should be reevaluated (*18*).

Although intermittent intrathecal (IT) injection of a particular enzyme has been cited as a way to overcome the blood–brain barrier, continuous IT infusion of that enzyme would be more physiologically appropriate. Responses in the brains of MPS type II mice to varying doses of continuous IT infusion of recombinant human IDS (rh-IDS) were investigated in MPS type II mice receiving three different doses (2.4, 4.8, and 12 mg/day) of rh-IDS for three weeks *via* osmotic pump (19). Results indicated that mice treated with 12 mg/day had decreased GAG concentrations compared to the untreated KO mouse group ($P < 0.003$). After three weeks of continuous IT ERT, the brain tissues of the KO mice treated with a high dose of IT had reduced vacuolation in the cerebral cortex, thalamus, and cerebellar cortex. The same was not observed in KO mice treated with a low or medium dose. Moreover, anti-NeuN signaling indicative of intact neurons was restored in the cortexes of the mice treated with a high dose. Continuous IT infusion of the deficient enzyme was effective at improving CNS defects in mice with MPS type II and may represent a beneficial therapy to treat neurological deterioration in patients with MPS type II.

6. ERT in South Korea

The treatment of MPS type II was palliative prior to the introduction of ERT. For over 10 years, ERT with recombinant human enzyme for MPS types I, II, and VI (Aldurazyme® for MPS type I, Elaprase® for MPS type II, Naglazyme® for MPS type VI) has been approved in the US, Europe, South Korea, and many other countries worldwide. The current authors have been actively involved in a phase III clinical trial of a recombinant enzyme for Morquio syndrome A. The drug is now permitted in South Korea and is expected to be commercially available within a year. Intravenously-infused enzymes are internalized *via* mannose 6 phosphate receptors located on the cell surface to reach their target site in the lysosomes and replace the defective enzymes (*20*). The earlier ERT is initiated, the better the potential outcome because of the irreversible nature of some of the abnormalities associated with MPS disorders (*21,22*). The benefits of ERT for certain MPS disorders may include improvements in joint mobility, walking ability, and pulmonary and respiratory function; a reduction in liver and spleen volume; and a significant reduction in urinary GAG excretion (*23-27*). When ERT is administered intravenously, the enzyme does not cross the blood–brain barrier at the labelled dose and the therapy has not yielded any neurocognitive benefits. The most common adverse events associated with ERT are infusion-related hypersensitivity reactions that can be characterized by flushing, headache, pyrexia, or urticaria. Such reactions are generally managed by slowing the infusion rate and administering antihistamines and/or steroids (*28*). However, life-threatening anaphylactic reactions can occur in patients receiving ERT. In a previous study (*29*), anaphylaxis associated with the infusion of idursulfase was mediated by anti-idursulfase IgE antibodies, which can be produced by *de novo* synthesis. The skin-prick test was useful at predicting the occurrence of anti-idursulfase IgE–mediated anaphylaxis during infusion. Therefore, the skin-prick test is usually performed before initiating ERT. Several patients with Hunter syndrome developed life-threatening anaphylactic reactions such as hypotension, blurred vision, and angioedema. All of the patients received ERT in accordance with the desensitization protocol over 48 hours a week in the early period, when they exhibited

severe anaphylaxis, and some of the patients were switched to another drug for ERT. Now, all of these patients are receiving ERT in accordance with general protocols and none have exhibited severe anaphylaxis.

7. Development of idursulfase beta and phase I/II clinical trials on idursulfase beta in South Korea

Successful clinical trials (*25,30*) have led to the approval of ERT with human recombinant idursulfase (Elaprase®, Shire Human Genetic Therapies, Lexington, MA) by the US Food and Drug Administration (FDA) in July 2006, and this therapy has been available in South Korea since 2009. Another drug for Hunter syndrome, idursulfase beta (Hunterase®, Green Cross Corp., Yongin, South Korea), was approved by the Korean FDA in January 2012. This drug is a recombinant protein that is produced by genetically engineered Chinese hamster ovary (CHO) cell lines. Idursulfase beta is produced in a serum-free medium *via* suspension cell culture and is purified in several chromatography steps. A number of chromatography and electrophoresis techniques have revealed the purity of the purified protein to be > 99.9%. Preclinical studies using a KO mouse model of MPS type II suggested that a course of 24 weeks of ERT with idursulfase beta (Hunterase) was effective at reducing urinary GAG excretion and GAGs stored in several tissues, including the liver, spleen, heart, lungs, and kidneys (unpublished data). A 24-week randomized, single-blinded, active comparator–controlled, phase I/II clinical trial of idursulfase beta was conducted to evaluate its efficacy and safety in the treatment of MPS type II patients. This study (*31*) was the first active comparator–controlled clinical trial of idursulfase beta for Korean male patients with MPS type II. The idursulfase beta treatment was well tolerated by Korean patients with MPS type II and resulted in a significant reduction in urinary GAG excretion as well as an improvement in the distance on the six-minute walking test when compared to the active comparator. The effect of the treatment on pulmonary function, cardiac function, and joint mobility was similar to that of the active comparator. A long-term clinical trial to establish the long-term efficacy and safety of idursulfase beta for the treatment of MPS type II is currently underway. However, further experiments will be needed, particularly in patients who have never received ERT. A considerable number of patients in South Korea are now being treated with Hunterase®. Hunterase has recently been exported to other countries in Asia and to the Middle East. In addition, a global clinical trial of Hunterase will soon begin.

8. The Asia-Pacific MPS Network (APMN)

Although individually rare, MPS disorders as a whole are highly prevalent, with an overall incidence of 1:22,000-52,000. Asia is the world's most populous continent, with approximately 4.3 billion people. Many patients may have gone undiagnosed or may be receiving minimal care in this region. In most countries, there is a lack of specialized healthcare personnel to provide adequate, comprehensive care for patients with MPS. Although the management of some clinical problems associated with the disease may seem routine, management is usually complicated and requires physicians' awareness of issues specific to the disease. Therefore, a multidisciplinary approach and the coordination of efforts by the professional, social, and governmental sectors are required. An important step is to establish an infrastructure of experts in each country and promote cooperation within the Asia-Pacific region in order to improve specialist training and communication. Given the need for a system of cooperation, the APMN was established by several MPS experts in South Korea, Japan, and Taiwan in January 2013. The four main objectives of the APMN are as follows: *1*) to organize an Asia-Pacific research network for MPS (establishing a registry and standard treatment guidelines); *2*) to understand the current state of the disease and exchange information on it; *3*) to provide support for preclinical studies related to MPS and patients with MPS/parents in the Asia-Pacific region; and *4*) to encourage and engage in an international exchange of younger doctors who are treating MPS patients. A survey to assess the current patterns of MPS diagnosis and treatment in the Asia-Pacific region should be conducted to identify gaps in knowledge and unmet needs that must be addressed and to provide opportunities for research on particularly relevant topics in the region. The professional knowledge and experience of MPS experts should be shared through international cooperation in order to provide better treatment to patients with MPS in Asia, in the Pacific region, and around the world. All of these efforts should be aimed at providing effective care for MPS patients. Recently, the APMN has been expanding through the participation of other Asian experts. The APMN developed an MPS-specific registry a year after its establishment.

9. The Asia-Pacific MPS Registry (APMR)

One of the obstacles to the identification, understanding, and treatment of MPS is the relative paucity of information. Therefore, regional and national disease registries are needed to facilitate the better understanding of the natural history of this clinically heterogeneous disease and to generate long-term data to evaluate existing and new therapies. One way that patients can take part in ongoing research efforts is through their enrolment in disease-specific registries. Observations based on these international registries will provide insights into the natural history of the disease and

Table 1. Recommended schedule of assessments in South Korea

Assessments	Initial	Every 3 mo	Every 6 mo	Every 12 mo
General				
Medical photo (if needed)	√		√ (1st)	
Height/weight/head circumference	√	√		
V/S(BP,RR,HR)	√	√ (weekly)		
P/Ex (including Tanner stage)	√	√ (weekly)		
N/Ex	√	√ (weekly)		
Laboratory test	√		√	
Urine GAG	√	√		
Current medication	√	√		
ERT				
Drug		√		
Dose		√		
Frequency		√		
Adverse reactions		√		
Premedication		√		
Clinical assessments				
Gastrointestinal system				
Abd US (hepatosplenomegaly)	√			√
Feeding problem (gastrostomy tube/L-tube)	√	√		
Umbilical/inguinal hernia	√	√ (weekly)		
Airway				
Pulmonary function test (if possible)	√			√
Respiratory assistance	√	√ (weekly)	√	
Number of bouts of pneumonia	√			
Sleep study (if needed)	√			√ (if needed)
Eye, Nose, & Throat			√ (or yearly)	
Audiometry	√		√ (or yearly)	
Airway patency	√		√	
Frequency of ear infections/surgery	√		√	
Placement and/or replacement of grommets	√			
Neurologic system			√	
Epilepsy medication	√			
MRI of brain	√			√ (if needed)
MRI of spine (if needed)	√			√ (if needed)
Cognitive testing (IQ/developmental milestone)	√			√
Bones & Joints				
Skeletal survey by X-ray	√		√	√ (if needed)
Surgical history	√		√ (or yearly)	
Range of motion of shoulder joint	√			
Median nerve conduction velocity (if needed)	√			√
6 min walking test	√			√
Cardiovascular system				
Echocardiogram/ECG	√			√
NT proBNP	√			√
Chest X-ray	√			√
Eye				
Visual acuity/ Visual field	√			√
Fundoscopy/ Retinoscopy (if needed)	√			√
Quality of life			√ (or yearly)	
Activities of Daily Living (FIM)	√			
Dental exam	√			√

Mo, month; V/S, vital sign; BP, blood pressure; HR, heart rate; P/Ex, physical examination; N/Ex, neurologic examination; ERT, enzyme replacement therapy; US, ultrasonography; IQ, intelligence quotient; ECG, electrocardiogram; FIM, functional independence measure

the long-term effects of various therapies. Such data can be used to help identify unmet patient needs and encourage further research. Registries have been established for MPS type I (*www.mpsiregistry.com*), MPS type II (*www.elaprase.com/patients_families/about_hunter/outcomes/*), MPS type IVA, and MPS type VI (*http://www.naglazyme.com/en/Clinical-resources/surveillance-program.aspx*), and the Morquio A Clinical Assessment Program has also been initiated. However, these registries are managed by pharmaceutical companies that make drugs for MPS patients. Moreover, they mainly include patients from Europe and the US, and most Asian patients with MPS have not been enrolled in these registries. The registration of patients and subsequent epidemiological research should be independent of any pharmaceutical

company in order to objectively evaluate the efficacy and side effects of ERT drugs. The APMR, an electronic remote data system, was established by key doctors in the APMN.

The healthcare systems in individual Asian-Pacific countries differ greatly in terms of their structure and access to diagnostic tools and treatment. Furthermore, there are large variations in insurance coverage in different countries and even in regions within the same country. In countries where ERT is not currently available, symptomatic management remains the primary treatment option. There is also substantial national variation in patterns of MPS monitoring. The APMR has been structured to accommodate different clinical practices in different countries/regions because data related to procedures that are not routinely performed in a particular country are sometimes requested. The APMR also includes patients who have not received ERT. The APMR will include patients with all types of MPS and it will act as a hub in global clinical trials of any new drugs for patients with MPS. The registration of patients with Hunter syndrome began in July 2014, and the APMR will be expanded into a global MPS registry (GMR) as the number of nations participating in the APMN increases.

10. The Korean Mucopolysaccharidosis Expert Council (KMEC)

Clinical and genetic characteristics and medical conditions differ in each country. A standard guideline for Korean patients with MPS was required for the appropriate evaluation of treatments and to guarantee the safety of patients. In addition, evidence of the need for treatment needed to be compiled. In light of these requirements, the KMEC was established by several MPS experts in South Korea in January 2013. The Korean guideline for Hunter syndrome was published in May 2014. Individual guidelines for other subtypes of MPS will be published regularly, and the recommended follow-up schedule for assessment of MPS is shown in Table 1.

11. The Korean MPS Symposium

An annual Korean MPS Symposium is held in South Korea with the support of the Korean Society of Inherited Metabolic Disease. The first Korean MPS Symposium was held in May 2002, while the most recent, the 13th Korean MPS Symposium, was held in May 2014. Initially, the symposium was more of a domestic conference. However, the scale of the symposium has expanded, and speakers and attendees now come from around the world. The attendees of the 13th Korean MPS Symposium not only came from Asia-Pacific countries but also from North and South America, Europe, and Africa. The symposium consisted of two sessions – a scientific session and a session for patients and families. In the academic session, many global experts on MPS presented clinical studies and up-to-date results from laboratory research. The 13th symposium, as an example, dealt with clinical issues, including early diagnosis, newborn screening, the long-term outcomes of ERT and hematopoietic stem cell transplantation, and brand new approaches being explored to address "hard-to-treat" organs such as the brain and bones. At the symposium, attendees were able to engage in detailed discussions and they had the opportunity to share their experiences with global experts. The family session provided time for family support in various areas and for Korean families of patients with MPS to become acquainted. This assembly of patients and family groups empowers offers support and advocacy.

In conclusion, the Korean MPS population has been discussed here both from the patient's perspective and also in terms of medical care and research. An organization like APMN is necessary because international cooperation and collaboration are needed to elucidate the mechanisms of rare diseases and to conduct clinical trials on those diseases. The collaboration between Japan, South Korea, and the other Asian countries will be of the utmost importance in the future.

Acknowledgements

This study was supported by a grant from the Samsung Medical Center [#GFO 1140061].

References

1. Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: The Metabolic and Molecular Bases of Inherited Disease. Scriver CR *et al*. (eds.). 7th ed. New York, McGraw-Hill, 1995.
2. Lin HY, Lin SP, Chuang CK, Niu DM, Chen MR, Tsai FJ, Chao MC, Chiu PC, Lin SJ, Tsai LP, Hwu WL, Lin JL. Incidence of the mucopolysaccharidoses in Taiwan, 1984-2004. Am J Med Genet A. 2009; 149A:960-964.
3. Kim CH, Hwang HZ, Song SM, Paik KH, Kwon EK, Moon KB, Yoon JH, Han CK, Jin DK. Mutational spectrum of the iduronate 2 sulfatase gene in 25 unrelated Korean Hunter syndrome patients: Identification of 13 novel mutations. Hum Mutat. 2003; 21:449-450.
4. Sohn YB, Ki CS, Kim CH, Ko AR, Yook YJ, Lee SJ, Kim SJ, Park SW, Yeau S, Kwon EK, Han SJ, Choi EW, Lee SY, Kim JW, Jin DK. Identification of 11 novel mutations in 49 Korean patients with mucopolysaccharidosis type II. Clin Genet. 2012; 81:185-190.
5. Lee IJ, Hwang SH, Jeon BH, Song SM, Kim JS, Paik KH, Kwon EK, Jin DK. Mutational analysis of the alpha-L-iduronidase gene in 10 unrelated Korean type I mucopolysaccharidosis patients: Identification of four novel mutations. Clin Genet. 2004; 66:575-576.
6. Park HD, Ko AR, Ki CS, Lee SY, Kim JW, Cho SY, Kim

SH, Park SW, Sohn YB, Jin DK. Five novel mutations of GALNS in Korean patients with mucopolysaccharidosis IVA. Am J Med Genet A. 2013; 161A:509-517.
7. Lachman RS, Burton BK, Clarke LA, Hoffinger S, Ikegawa S, Jin DK, Kano H, Kim OH, Lampe C, Mendelsohn NJ, Shediac R, Tanpaiboon P, White KK. Mucopolysaccharidosis IVA (Morquio A syndrome) and VI (Maroteaux-Lamy syndrome): Under-recognized and challenging to diagnose. Skeletal Radiol. 2014; 43:359-369.
8. Sohn YB, Park HD, Park SW, Kim SH, Cho SY, Ko AR, Ki CS, Yeau S, Jin DK. A Korean patient with Morquio B disease with a novel c.13_14insA mutation in the GLB1 gene. Ann Clin Lab Sci. 2012; 42:89-93.
9. Sohn YB, Choi EW, Kim SJ, Park SW, Kim SH, Cho SY, Jeong SI, Huh J, Kang IS, Lee HJ, Paik KH, Jin DK. Retrospective analysis of the clinical manifestations and survival of Korean patients with mucopolysaccharidosis type II: Emphasis on the cardiovascular complication and mortality cases. Am J Med Genet A. 2012; 158A:90-96.
10. Kwon JY, Ko K, Sohn YB, Kim SJ, Park SW, Kim SH, Cho SY, Jin DK. High prevalence of carpal tunnel syndrome in children with mucopolysaccharidosis type II (Hunter syndrome). Am J Med Genet A. 2011; 155A:1329-1335.
11. Cho SY, Huh R, Chang MS, Lee J, Kwun Y, Maeng SH, Kim SJ, Sohn YB, Park SW, Kwon EK, Han SJ, Jung J, Jin DK. Impact of enzyme replacement therapy on linear growth in Korean patients with mucopolysaccharidosis type II (Hunter syndrome). J Korean Med Sci. 2014; 29:254-260.
12. Sohn YB, Kim SJ, Park SW, Park HD, Ki CS, Kim CH, Huh SW, Yeau S, Paik KH, Jin DK. A mother and daughter with the p.R443X mutation of mucopolysaccharidosis type II: Genotype and phenotype analysis. Am J Med Genet A. 2010; 152A:3129-3132.
13. Lee NH, Cho SY, Maeng SH, Jeon TY, Sohn YB, Kim SJ, Park HD, Jin DK. Clinical, radiologic, and genetic features of Korean patients with Mucopolysaccharidosis IVA. Korean J Pediatr. 2012; 55:430-437.
14. Mahalingam K, Janani S, Priya S, Elango EM, Sundari RM. Diagnosis of mucopolysaccharidoses: How to avoid false positives and false negatives. Indian J Pediatr. 2004; 71:29-32.
15. Jung SC, Park ES, Choi EN, Kim CH, Kim SJ, Jin DK. Characterization of a novel mucopolysaccharidosis type II mouse model and recombinant AAV2/8 vector-mediated gene therapy. Mol Cells. 2010; 30:13-18.
16. Hong SH, Chu H, Kim KR, *et al*. Auditory characteristics and therapeutic effects of enzyme replacement in mouse model of the mucopolysaccharidosis (MPS) II. Am J Med Genet A. 2012; 158A:2131-2138.
17. Lee SC, Lee J, Jin DK, Kim JS, Jeon ES, Kwun YH, Chang MS, Ko AR, Yook YJ, Sohn YB. Improvement of cardiac function by short-term enzyme replacement therapy in a murine model of cardiomyopathy associated with Hunter syndrome evaluated by serial echocardiography with speckle tracking 2-D strain analysis. Mol Genet Metab. 2014; 112:218-223.
18. Ahn SY, Chang YS, Sung DK, Ko AR, Kim CH, Yoo DK, Lim KH, Sohn YB, Jin DK, Park WS. High-dose enzyme replacement therapy attenuates cerebroventriculomegaly in a mouse model of mucopolysaccharidosis type II. J Hum Genet. 2013; 58:728-733.
19. Sohn YB, Lee J, Cho SY, Kim SJ, Ko AR, Nam MH, Jin DK. Improvement of CNS defects *via* continuous intrathecal enzyme replacement by osmotic pump in mucopolysaccharidosis type II mice. Am J Med Genet A. 2013; 161A:1036-1043.
20. Kakkis ED. Enzyme replacement therapy for the mucopolysaccharide storage disorders. Expert Opin Investig Drugs. 2002; 11:675-685.
21. McGill JJ, Inwood AC, Coman DJ, Lipke ML, de Lore D, Swiedler SJ, Hopwood JJ. Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age – A sibling control study. Clin Genet. 2010; 77:492-498.
22. Schulze-Frenking G, Jones SA, Roberts J, Beck M, Wraith JE. Effects of enzyme replacement therapy on growth in patients with mucopolysaccharidosis type II. J Inherit Metab Dis. 2011; 34:203-208.
23. Wraith JE, Beck M, Lane R, van der Ploeg A, Shapiro E, Xue Y, Kakkis ED, Guffon N. Enzyme replacement therapy in patients who have mucopolysaccharidosis I and are younger than 5 years: Results of a multinational study of recombinant human alpha-L-iduronidase (laronidase). Pediatrics. 2007; 120:e37-46.
24. Clarke LA, Wraith JE, Beck M, Kolodny EH, Pastores GM, Muenzer J, Rapoport DM, Berger KI, Sidman M, Kakkis ED, Cox GF. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics. 2009; 123:229-240.
25. Muenzer J, Wraith JE, Beck M, *et al*. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med. 2006; 8:465-473.
26. Muenzer J, Beck M, Eng CM, *et al*. Long-term, open-labeled extension study of idursulfase in the treatment of Hunter syndrome. Genet Med. 2011; 13:95-101.
27. Muenzer J, Beck M, Giugliani R, Suzuki Y, Tylki-Szymanska A, Valayannopoulos V, Vellodi A, Wraith JE. Idursulfase treatment of Hunter syndrome in children younger than 6 years: Results from the Hunter Outcome Survey. Genet Med. 2011; 13:102-109.
28. Burton BK, Whiteman DA, Investigators HOS. Incidence and timing of infusion-related reactions in patients with mucopolysaccharidosis type II (Hunter syndrome) on idursulfase therapy in the real-world setting: A perspective from the Hunter Outcome Survey (HOS). Mol Genet Metab. 2011; 103:113-120.
29. Kim J, Park MR, Kim DS, Lee JO, Maeng SH, Cho SY, Han Y, Ahn K, Jin DK. IgE-mediated anaphylaxis and allergic reactions to idursulfase in patients with Hunter syndrome. Allergy. 2013; 68:796-802.
30. Muenzer J, Gucsavas-Calikoglu M, McCandless SE, Schuetz TJ, Kimura A. A phase I/II clinical trial of enzyme replacement therapy in mucopolysaccharidosis II (Hunter syndrome). Mol Genet Metab. 2007; 90:329-337.
31. Sohn YB, Cho SY, Park SW, Kim SJ, Ko AR, Kwon EK, Han SJ, Jin DK. Phase I/II clinical trial of enzyme replacement therapy with idursulfase beta in patients with mucopolysaccharidosis II (Hunter syndrome). Orphanet J Rare Dis. 2013; 8:42.

(Received July 22, 2014; Accepted August 13, 2014)