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Clinical characteristics and effects of enzyme replacement therapy with elosulfase alfa in Korean patients with mucopolysaccharidosis type IVA

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ABSTRACT

Mucopolysaccharidosis type IVA (MPS IVA) is a rare autosomal recessive disorder caused by a deficiency in *N*-acetylgalactosamine-6-sulfatase, which results in skeletal and connective tissue abnormalities, as well as various non-skeletal manifestations. Although enzyme replacement therapy (ERT) is recommended as the first-line treatment, the outcomes of ERT on bone pathology remain controversial. We report clinical characteristics and outcomes of ERT in 9 patients with MPS IVA (6 males and 3 females) from 7 unrelated families. During ERT, results from pulmonary function tests, echocardiography, the 6-min walk test, and the Functional Independence Measure were monitored biannually. Anthropometric data were compared with previously reported growth charts of subjects with MPS IVA.

Among the 9 patients (5 severe, and 4 slowly progressive form), 7 patients (5 severe, 2 slowly progressive) commenced ERT at a median age of 3.8 years (range: 0.8–13.7 years) and were treated for a median duration of 1.9 years (range: 1.2–5.7 years). Mean height standard deviation scores using MPS IVA growth charts were + 0.4 (+0.0 in severe phenotypes) at initiation and + 0.7 (+0.2 in severe phenotypes) at the last follow-up. Four patients with severe phenotypes underwent surgery for cervical myelopathy and 1 patient with a slowly progressive phenotype underwent a bilateral pelvic osteotomy for hip pain during ERT. The parameters of pulmonary and heart function, endurance, and Functional Independence Measure scores were maintained or increased after ERT. Overall, ERT was well tolerated without deterioration of cardiorespiratory and functional outcomes during treatment, although skeletal outcomes, including growth, were limited.

1. Introduction

Mucopolysaccharidosis type IVA (MPS IVA, Morquio A syndrome, OMIM #253000) is a rare autosomal recessive metabolic disorder caused by deficiency of the lysosomal enzyme, *N*-acetylgalactosamine-6-sulfatase (GALNS), encoded by the *GALNS* gene [1]. The prevalence of MPS IVA ranges from 1 in 76,000 live births in Northern Ireland to 1 in 640,000 live births in Western Australia [2,3]. In the absence of GALNS, catabolism of keratan sulfate and chondroitin-6-sulfate is impaired, resulting in lysosomal accumulation of glycosaminoglycans (GAGs) throughout the body, mainly in cartilage and bone [4].

MPS IVA is characterized by skeletal and connective tissue abnormalities as well as non-skeletal manifestations, including respiratory and cardiac disease, spinal cord compression, hearing loss, and corneal opacity [5]. The onset of symptoms and the clinical course of affected patients are heterogeneous, but multisystem impairments gradually develop in most cases [6]. In patients with severe phenotypes, paralysis due to cervical myelopathy, respiratory insufficiency, and cardiac dysfunction may cause premature mortality [7]. Patients with slowly progressive phenotype have near-normal life expectancies but still experience limitations in activities of daily living and decreased quality of life, due to short stature and progressive musculoskeletal impairments [7].

Enzyme replacement therapy (ERT) was first introduced in 2014, and

Abbreviations: MPS IVA, Mucopolysaccharidosis type IVA; ERT, enzyme replacement therapy; GALNS, *N*-acetylgalactosamine-6-sulfatase; GAGs, glycosaminoglycans; 6MWT, 6-min walk test; FIM, (Functional Independence Measure); SDS, standard deviation score; SDS_K, standard deviation score for height based on Korean National Growth Charts; SDS_M, standard deviation score for height based on untreated MPS IVA growth reference.

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international management guidelines for MPS IVA recommend elosulfase alfa as a first-line treatment that targets the underlying pathology [8]. Its efficacy and safety were demonstrated in several clinical trials [9–11]. Multiple studies have reported the positive impact of long-term elosulfase alfa treatment on quality of life, endurance, and pulmonary function test (PFT) scores [12–14]. However, there is limited evidence that ERT has a positive impact on bone lesions and skeletal dysplasia in patients with MPS IVA [15]. In Korea, there are only 2 case series describing the clinical manifestations of a total of 13 patients with MPS IVA, which were published before the introduction of ERT [16,17]. In this study, we investigated the phenotypic and genetic features of 9 Korean patients with MPS IVA and evaluated the impact of ERT on the clinical outcomes of 7 patients according to disease severity.

2. Materials and methods

2.1. Subjects

Nine patients from 7 unrelated families were diagnosed with MPS IVA using biochemical and molecular genetic tests at Seoul National University Children's Hospital between 2011 and 2022. Clinical data were retrospectively collected from electronic medical records. The phenotypic severity of disease was classified into two categories according to baseline height measured before ERT initiation: severe (below the 75th percentile on the MPS IVA growth chart of each sex) and slowly progressive form (above the 75th percentile on the MPS IVA growth chart) [18,19]. Height (cm) was measured using a Harpenden Stadiometer (Holtain Ltd., Crymych, Wales, UK), and standard deviation scores (SDS) for height were assigned based on the 2017 Korean National Growth Charts (SDS_K) and MPS IVA growth references (SDS_M) [20,21]. The target adult height (TAH) was calculated by adding and subtracting 6.5 cm to the mean of parental heights in boys and girls, respectively [22]. Growth improvement was defined as greater than +1.0 increase in height SDS at the last measurement from baseline compared with patients with untreated MPS IVA. This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB number 2103–200-1208). The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Biochemical and genetic analysis

Excretion of urinary GAGs was qualitatively or quantitatively measured using the toluidine blue spot test or liquid chromatography-mass spectrometry [23,24]. GALNS activity was assessed in peripheral blood leukocytes using a fluorometric assay [25]. Informed consent for molecular genetic analysis was obtained from the parent(s) of each patient. Genomic deoxyribonucleic acid was isolated from peripheral blood leukocytes. Using Sanger sequencing for the *GALNS* gene or target panel sequencing for mucopolysaccharidoses, all patients were confirmed to harbor homozygous or compound heterozygous variants of the *GALNS* gene. Segregation analysis was performed for each family to verify the identified variants located in *trans*.

2.3. Investigations during ERT

Seven patients were treated with weekly infusions of elosulfase alfa (Vimizim®, 2.0 mg/kg). Before and during initiation of ERT, skeletal findings were examined by orthopedic surgeons, and plain radiographs of the hips, knees, ankles, and spines were obtained at least annually. Magnetic resonance imaging (MRI) of the cervical spine was performed before the initiation of ERT and repeated depending on the presence of symptoms or signs of cervical myelopathy. PFT values, including forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1), were collected in 2 patients who were aged over 6 years [26]. Endurance was assessed by measuring distance achieved during the 6-min walk test (6MWT) in patients who were able to walk independently [27]. Functional independence was assessed using the Functional Independence Measure (FIM) for children, which consists of 18 items in 3 domains (self-care, mobility, and cognition) to constitute a total score out of 126 [28]. Anthropometric data, echocardiography results, PFTs, 6MWT results, and FIM scores were evaluated biannually. Eye and ear-nose-throat examinations were performed in all patients before ERT and at least annually thereafter. Age-appropriate auditory evaluation was conducted and included pure tone audiometry and the auditory brainstem response test.

2.4. Statistical analysis

SPSS for Windows (version 21.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For continuous variables, the Shapiro-Wilk test was performed to assess normality. Continuous variables with a normal distribution are presented as mean values with standard deviations (SD), while variables without a normal distribution are presented as median values with ranges. The differences in the residual GALNS activity between severe and slowly progressive phenotype were assessed using the Mann-Whitney *U* test. The ERT response in each patient was analyzed using the Wilcoxon signed-rank test. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

The baseline characteristics of 9 patients with MPS IVA are summarized in Table 1. Based on their baseline heights, 5 patients (P1, P2, P3, P4, and P5) were classified into the severe phenotype group, and 4 patients (P6, P7, P8, and P9) were classified into the slowly progressive phenotype group. Median age at diagnosis was 4.9 years (range: 0.6–12.0 years) and median follow-up duration was 3.7 years (range: 1.4–28.4 years). Other than patient P5, who was diagnosed through family screening, patients were diagnosed after being reviewed at the orthopedic clinic because of skeletal issues. All 9 patients had various skeletal manifestations and radiologic abnormalities at the time of diagnosis. Common skeletal findings included kyphosis ($n = 6$), anterior beaking of the thoracolumbar spine (n = 6), platyspondyly ($n = 5$), acetabular dysplasia of the hip ($n = 4$), gait abnormality (n = 4), genu valgum (n = 4), pectus carinatum ($n = 3$), short stature (n = 3), and cervical stenosis (n = 3). Frequently associated non-skeletal findings included recurrent otitis media ($n = 6$), middle ear effusion (n = 3), and hepatomegaly ($n = 2$).

Residual GALNS activity was inversely correlated with clinical severity (median 0.4 nmol·mg^{-1}·17 h^{-1} in the severe group vs. 2.9 nmol·mg^{-1}·17 h^{-1} in the slowly progressive group; $p = 0.016$). Twelve different *GALNS* mutations were identified in 14 alleles from the 7 unrelated families, including 4 novel pathogenic or likely pathogenic variants: c.167C > T (p.T56I) (likely pathogenic; PM2 + PM3 + PP3 + PP4), c.1234_1240delTTCAGAC (p.F412Rfs*27) (pathogenic; PVS1 + PM2 + PP4), c.1426C > T (p.Q476*) (pathogenic; PVS1 + PM2 + PP4), and c.707A > C (p.H236P) (likely pathogenic; PM2 + PM6 + PP3 + PP4).

3.2. Skeletal outcomes in ERT-treated patients

Seven patients (5 severe, 2 slowly progressive) commenced ERT at a median age of 3.8 years (range: 0.8–13.7 years) and were treated for a median duration of 1.9 years (range: 1.2–5.7 years). Two siblings with slowly progressive phenotypes (P8 and P9 in Family 7), who reached their final heights, declined to receive ERT. Overall mean change in height SDS during ERT was +0.3 (from +0.4 to +0.7) SDS_M and − 2.0 (from −0.9 to −2.9) SDS_K, while it was +0.2 (from +0.0 to +0.2) SDS_M and − 2.1 (from −0.5 to −2.6) SDS_K in the severe phenotype subgroup. However, changes in height SDS_M during ERT were not

Table 1
Baseline clinical, biochemical, and molecular characteristics of patients.

Family no.	Case no.	Phenotype	Sex	Age at Dx (yrs)	TAH (SDS_K)	Ht (SDS_K)	Ht (SDS_M)	Symptoms/signs at Dx		GALNS activity[a]	*GALNS* variants
								Skeletal	Non-skeletal		
1	P1	Severe	M	1.0	−0.3	+0.4	−0.2	KP, AD, GV, AI	CF, IH, ME, RO, UH	0.4	c.374C > T (p.P125L) (homo)
2	P2	Severe	M	1.9	−0.1	+0.3	+0.5	AD, KP, AD, CM, CS, CV, GV, KC, PC	GLV, HM, RO	0.5	c.167C > T (p.T56I)[b]; c.1234_1240delTTCAGAC (p.F412Rfs*27)[b]
3	P3	Severe	F	3.7	−0.3	−2.8	−0.1	AI, KP, AD, CS, GV, PE, PV, UW	ME, RO	0.4	c.451C > A (p.P151T); c.319G > A (p.A107T)
4	P4	Severe	M	5.2	−1.0	−2.6	+0.2	KP, AD, CM, CS, PC, UW	CC, ME, RO	0.2	c.752G > A (p.R251Q); c.1426C > T (p.Q476*)[b]
	P5	Severe	F	0.6	−1.0	+2.4	−0.4	KP, AD	–	0.1	
5	P6	SP	F	7.2	−0.2	−2.1	+1.6	AD, KP, PC, GV, DFH, SL	CHL, HM, RO	2.2	c.1019G > A (p.G340D); c.725C > G (p.S242C)
6	P7	SP	M	12.0	−1.7	−1.8	+1.3	AD, KP	RO	3.7	c.281G > A (p.R94H); c.707A > C (p.H236P)[b]
7	P8	SP	M	4.9	−0.4	+0.8	+2.1	GV, KP, AD, PV, CV, DFH	–	3.2	c.1462G > A (p.V488M) (homo)
	P9	SP	M	6.1	−0.4	+2.8	+3.0	AD, DFH, GV, KP	–	2.6	

Abbreviations: Dx, diagnosis; TAH, target adult height; SDS_K, standard deviation score based on Korean National Growth Charts; Ht, height; SDS_M, standard deviation score based on untreated MPS IVA growth reference; M, male; N/A, not available; F, female; KP, kyphosis; CF, coarse face; IH, inguinal hernia; ME, middle ear effusion; RO, recurrent acute otitis media; UH, umbilical hernia; AD, acetabular dysplasia of hip; CM, cervical myelopathy; CS, cervical stenosis; CV, cubitus valgus; GA, gait abnormality; GV, genu valgum; KC, knee flexion contracture; PC, pectus carinatum; GLV, globular left ventricle; HM, hepatomegaly; AI, atlantoaxial instability; PE, pectus excavatum; PV, pes valgus; UW, ulnar deviation of wrist; CC, corneal clouding; SP, slowly progressive; SL, scoliosis; CHL, conductive hearing loss; DFH, dysplastic femoral head.

[a] Reference ranges are 18.6–61.8 nmol·mg^{-1}·17 h^{-1} in leukocytes.

[b] Novel variants.

statistically significant ($p = 0.395$). Two girls (P5 and P6) demonstrated an increase in height SDS_M of greater than +1.0 (+1.5 in P5 and + 1.3 in P6) (Fig. 1). P5, who was diagnosed through family screening and asymptomatic at diagnosis, commenced ERT at 0.8 years of age and maintained normal growth comparable to that of age- and sex-matched healthy controls (from +2.4 to +0.2 SDS_K) until the last follow-up. However, for P6, growth rapidly decreased after puberty compared to that for healthy controls, from −2.9 to −3.9 SDS_K (Table 2).

Four patients with severe phenotypes (P1, P2, P3, and P4) showed significant cervical stenosis with or without myelopathy on MRI and underwent cervical spinal surgery at a median age of 3.5 years (range: 2.4–5.4 years) (Fig. 2A and B). Three patients (P2, P3, and P4) required surgical decompression at diagnosis, and patient P1 was diagnosed with progressive cervical spinal cord compression during ERT, requiring C1 laminoplasty 25 months after ERT initiation. To date, none of these 4 patients have shown neurologic deterioration after surgical intervention. Bilateral hip dysplasia and subluxation were found in 5 patients (3 with severe phenotypes [P1, P2, and P3], 2 with slowly progressive phenotypes [P6 and P7]) during ERT. Of these, P6 underwent staged bilateral salvage surgery for hip dysplasia 4.0 years after ERT initiation (Fig. 2C). Four patients with severe phenotypes (P1, P2, P3, and P4) had genu valgum (Fig. 2D), which was either newly developed or progressed during ERT in 2 of these patients.

3.3. Non-skeletal outcomes in ERT-treated patients

All 7 ERT-treated patients maintained a normal left ventricular ejection fraction without valvular abnormalities during ERT. No acute respiratory events were observed in any patient. Two patients over 6 years of age (P6 and P7) were regularly followed up with PFTs. FVC and FEV_1 values remained normal during a median ERT duration of 5.7 years. Among the 5 patients who were able to walk at the time of diagnosis, the median 6MWT distance significantly increased from 120 m at baseline to 300 m at the last follow-up, across a median ERT duration of 3.8 years ($p = 0.043$). Median FIM scores also significantly increased in 7 ERT patients, from 46 at baseline to 68 at the last follow-up ($p = 0.018$) (Table 3).

In terms of ophthalmic abnormalities, 1 patient with severe phenotype (P4) had mild corneal clouding in both eyes at the initiation of ERT, which did not deteriorate during 1.3 years of follow-up. One patient with slowly progressive phenotype (P7) had no corneal clouding at the initiation of ERT, but developed mild corneal clouding in both eyes after 3.5 years of ERT. However, the lesions resolved 1 year later. Visual acuity was not significantly affected in any of the patients treated with ERT. In terms of otorhinolaryngologic abnormalities, all but the youngest patient (P5) had a history of recurrent episodes of otitis media before ERT initiation. One patient with slowly progressive phenotype (P6) suffered from obstructive sleep apnea at diagnosis and underwent tonsillectomy and adenoidectomy 0.7 years after ERT initiation. Conductive hearing loss due to middle ear effusion was noted in 2 patients (40/40 dB in P1 and 10/30 dB in P6). P1 required hearing aids 2.3 years after ERT initiation.

4. Discussion

This is the first report of ERT outcomes in a sample of Korean patients with MPS IVA. In our patients, the parameters of endurance and functional independence was increased during ERT. However, with the exception of 2 patients, our patients did not exhibit significant height change compared with the growth chart of untreated MPS IV patients. In addition, various skeletal problems did not significantly improve, such that 71.4% of patients required orthopedic surgery during ERT.

The finding that patients continued to exhibit poor growth during ERT is consistent with a previously published study of 67 patients with MPS IVA [29]. In this study, patients with MPS IVA treated with ERT showed a reduced pubertal growth spurt similar to untreated patients, reaching final adult heights at approximately 10 years of age [29]. With regards to 2 siblings in our study (P4 and P5 in Family 4), the growth of the younger sibling, who commenced ERT at 0.8 years of age, did not differ from their healthy peers until 2.0 years of age. Current data on

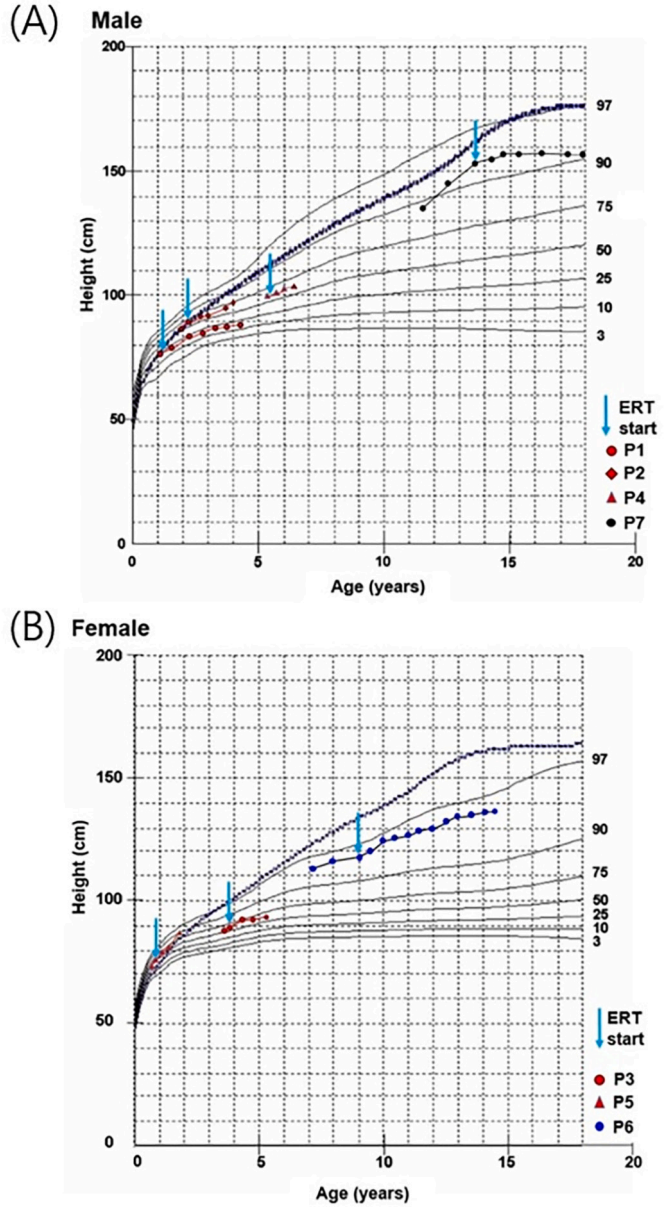

Fig. 1. Height of patients during follow-up, plotted on growth charts of MPS IVA. (A) Height change in boys with MPS IVA. (B) Height change in girls with MPS IVA.

height outcomes in patients who commenced ERT before 1.0 year of age are lacking. A recent longitudinal study on 2 siblings with MPS IVA reported a limited effect of ERT on growth during 4.5 years of treatment, even in a younger sibling who began ERT at 11 months of age, suggesting a major change in growth velocity around the age of 2 years [30]. However, growth was less deviated from the curve in the younger sibling than in the older sibling, who commenced ERT at 54 months of age, which suggests ERT has some beneficial effect on growth outcomes when initiated at a younger age [30].

Cervical spine involvement, particularly instability and compression at the C1-C2 level, is a near-universal finding in patients with MPS IVA, which predisposes to myelopathy, paralysis, and sudden death [31]. Recent consensus-based recommendations have suggested screening for spinal cord injury by performing annual spinal MRIs and have emphasized the importance of timely interventions to avoid irreversible damage [8]. In our patients, 4 out of 5 patients (80%) with severe phenotypes underwent cervical decompression surgery due to cervical

Table 2
Skeletal outcomes with ERT.

Family no.	Case no.	Phenotype	Sex	ERT									Orthopedic surgery		
				Age_i (yrs)	Ht_i (SDS_K)	Ht_i (SDS_M)	Age_l (yrs)	Ht_l (SDS_K)	Ht_l (SDS_M)	GV_1y (cm/yr)	GV_tot (cm/yr)	Tx duration (yrs)	Tx status	Age at surgery (yrs)	Operation
1	P1	Severe	M	1.2	+0.4	−0.2	4.7	−4.2	−0.8	5.0	3.3	3.5	OG	3.3	C1 LP
2	P2	Severe	M	2.1	+0.3	+0.5	4.0	−1.4	+0.7	2.3	4.1	1.9	OG	2.4	C1 LP
3	P3	Severe	F	3.8	−2.8	−0.1	5.3	−4.2	−0.2	3.1	2.6	1.5	OG	3.7	C1 LP
4	P4	Severe	M	5.4	−2.6	+0.2	6.7	−3.5	+0.1	2.5	3.2	1.3	OG	5.4	C1 LP
	P5	Severe	F	0.8	+2.4	−0.4	2.0	+0.2	+1.1	10.4	10.4	1.2	OG	–	–
5	P6	SP	F	9.0	−2.9	+1.3	14.6	−3.9	+2.6	6.5	3.5	5.6	OG	13.0	Pelvic osteotomy (sequential bilateral)
6	P7	SP	M	13.7	−1.4	+1.6	19.4	−3.1	+1.7	3.5	1.0	5.7	OG	–	–
7	P8	SP	M	N/A	N/A	N/A	33.3	−3.8	+1.5	N/A	N/A	N/A	NT	–	–
	P9	SP	M	N/A	N/A	N/A	30.6	−4.3	+1.4	N/A	N/A	N/A	NT	–	–

Abbreviations: ERT, enzyme replacement therapy; Age_i, age at initiation; Ht_i, height at initiation; SDS_K, standard deviation score based on Korean National Growth Charts; SDS_M, standard deviation score based on untreated MPS IVA growth reference; Age_l, age at last visit; Ht_l, height at last visit; GV_1y, growth velocity during the first-year after ERT; GV_tot, growth velocity during total ERT periods; Tx, treatment; OG, ongoing; C1 LP, laminoplasty of C1(atlas); SP, slowly progressive; N/A, not available; NT, not treated.
The cells with "–", imply that orthopedic surgery was not done for the patient.
In case of P8 and P9 who were not treated with ERT, Age_l, Ht_l (SDS_K), and Ht_l (SDS_M) are data from last visit, not during ERT.

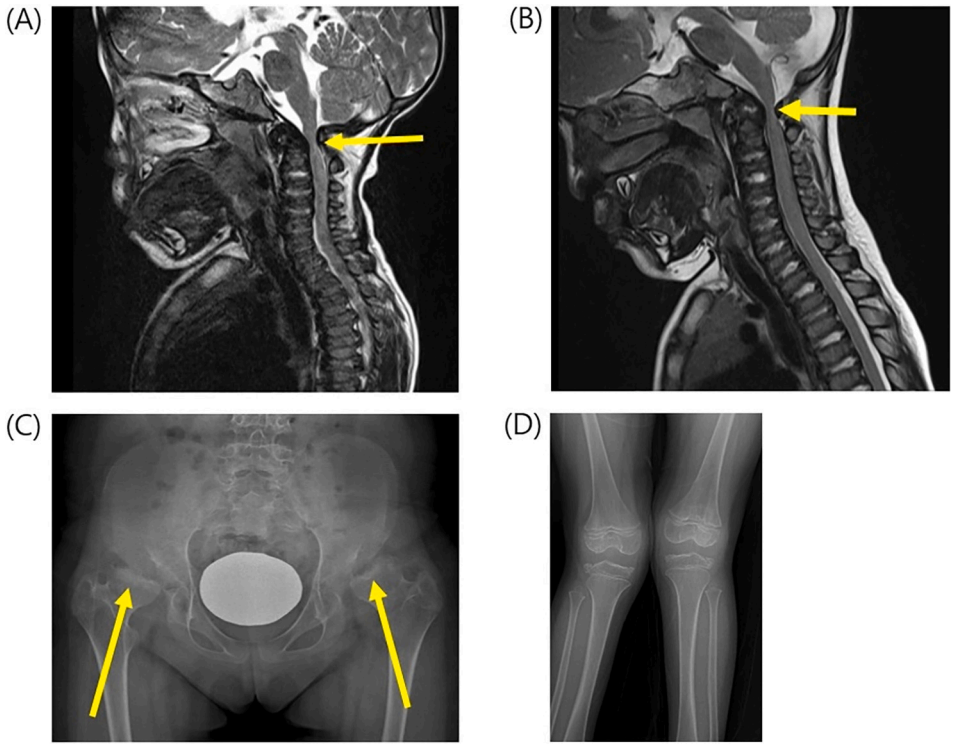

Fig. 2. Radiologic examination of patients with MPS IVA. (A) C-spine MRI of a 3.1-year-old boy (P1), showing indentation of the spinal cord at C1 by arch posterior side during flexion. (B) C-spine MRI of a 2.0-year-old boy (P2), showing a prominent C2 cartilage bump with narrowed spinal canal at the craniocervical junction. (C) Hip radiograph of a 12.2-year-old girl (P6), showing bilateral hip subluxation and deformed femoral heads. (D) Standing knee X-ray of a 4.7-year-old girl (P3), showing dysplastic epiphyses of the proximal tibia and genu valgum.

Table 3
Non-skeletal outcomes with ERT.

Family no.	Case no.	Phenotype	Sex	Age_i (yrs)	Age_l (yrs)	LVEF (%)		FVC (%)/FEV_1 (%)		6MWT (m)		FIM score	
						Baseline	Latest	Baseline	Latest	Baseline	Latest	Baseline	Latest
1	P1	Severe	M	1.2	4.1	66.1	65.4	N/A	N/A	N/A	100	28	57
2	P2	Severe	M	2.1	4.0	63.5	58.7	N/A	N/A	250	300	46	62
3	P3	Severe	F	3.8	5.3	63.0	62.2	N/A	N/A	25	50	55	68
4	P4	Severe	M	5.4	6.4	71.0	65.9	N/A	N/A	250	350	91	97
	P5	Severe	F	0.8	1.8	68.3	73.4	N/A	N/A	N/A	N/A	26	33
5	P6	Slowly progressive	F	9.0	14.5	64.6	59.3	130/131	121/117	120	334	46	103
6	P7	Slowly progressive	M	13.7	19.3	69.5	64.5	109/105	129/118	0	294	43	95

Abbreviations: Age_i, age at initiation of ERT; Age_l, age at last evaluation; LVEF, left ventricular ejection fraction; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; 6MWT, 6-min walk test; FIM, functional independence measure; N/A, not available.

spinal cord compression or C1-C2 subluxation, at the median age of 3.5 years (range: 2.4–5.4 years). In a study published before the era of ERT, 75% of 20 patients with severe phenotypes underwent cervical spinal surgery at age 7.9 years (range: 2–39 years) [32]. The earlier age of cervical spinal surgery in our patients may be explained by routine screening using spinal MRI, as well as the earlier age of diagnoses in the present study. Hip dysplasia with or without subluxation (71.4%) and valgus deformity of the knees (57.1%) were also common in our patients, and one of our patients with slowly progressive phenotype underwent surgery for bilateral hip dysplasia during ERT at the age of 13 years (4 years after ERT initiation). Longitudinal data are needed to determine long-term skeletal and neurologic outcomes in patients treated with ERT.

Cardiorespiratory function was not deteriorated in our patients during ERT, which is in line with previous reports [8,14,15,33]. All patients treated with ERT maintained acceptable left ventricular systolic function without meaningful valvular abnormalities during treatment, regardless of disease severity. Although baseline PFT results were available in only 2 patients because of the minimum age needed to cooperate with the test, FVC and FEV_1 remained within the normal range during follow-up of these patients. In the literature, an open-label, multicenter, phase 3 extension study reported that long-term ERT over 120 weeks was associated with sustained improvements in respiratory function regardless of age [10]. On the other hand, another study showed a gradual decline in lung function in both treated and untreated patients over 9 years of follow-up [34]. In the present study, the 6MWT distance (a measure of endurance) and FIM scores (a measure of functional independence) was increased in ERT-treated patients, consistent with previous studies [14,35,36]. However, the 6MWT distance at the last follow-up was shorter in our patients than the report in UK healthy children [37]. The increase in endurance in our study may have been overestimated, given that there is a rapid improvement in 6WMT results with age in healthy children aged 4 to 7 years [37]. Similarly, the increase in FIM scores during studied period is likely partially due to natural cognitive and motor development [38].

This study has several limitations. First, due to the small number of study participants and relatively short ERT duration in some patients, it was difficult to draw any conclusion regarding the long-term ERT outcomes. As current evidence on the impact of ERT was drawn primarily from patients starting ERT at the age of 5 years or more, further longitudinal studies are necessary in patients with MPS IVA who commenced ERT at an earlier age. Second, we could not evaluate patient reported outcomes other than FIM scores and quality of life due to the retrospective study design. However, our study is the first to report ERT

outcomes in Korean patients with MPS IVA. Moreover, detailed data on clinical manifestations and outcomes gathered through a multidisciplinary approach were presented in a relatively young patient cohort with good compliance, including data on siblings.

In conclusion, ERT was well tolerated in our MPS IVA patient cohort, with maintenance of cardiorespiratory function and increase in endurance, and functional independence. Although there were limited effects on skeletal manifestations, including effects on height, increase in height SDS_M of the youngest patient after treatment suggests a possible positive impact on growth outcomes if ERT is commenced from an early age. Further longitudinal studies are warranted to evaluate ERT outcomes, especially in patients who commenced treatment at an early age or when asymptomatic.

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CRediT authorship contribution statement

Seung Hoon Lee: Data curation, Visualization, Formal analysis, Writing – original draft. **Hwa Young Kim:** Data curation, Visualization, Methodology, Writing – review & editing. **Tae-Joon Cho:** Investigation, Writing – review & editing. **Hyoungmin Kim:** Investigation. **Jung Min Ko:** Investigation, Conceptualization, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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