

국내 6형 뮤코다당증의 임상 양상, 분자유전학적 특징 및 효소치료의 효과에 대한 고찰

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Clinical Features, Molecular Analysis, and Outcome of ERT in Korean Patients with Mucopolysaccharidosis Type VI

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Mucopolysaccharidosis type VI (MPS VI) is a rare disease caused by the mutation of ARSB with prevalence range from 1/5,000 in northeast Brazil to 1/2,057,529 births in Czech Republic. In Asia, there is only one published figure in Taiwan of about 1/833,000 births. The exact prevalence in the Korean population is unknown, but we estimated the incidence of MPS VI is about 0.03/100,000 live births. Enzyme replacement therapy (ERT) with recombinant human Arylsulfatase B (rhASB) is a modality for the treatment of MPS VI that reduces the excretion of urine glycosaminoglycan (GAG) and improves joint motion, pulmonary function, and endurance. We presented the clinical features, molecular analysis and outcome of ERT in three Korean MPS VI patients. All patients had the typical characteristic clinical features of MPS IV. Short stature, dysostosis multiplex, corneal opacity and valvular heart disease were found at first presentation, while restrictive lung disease and carpal tunnel syndrome developed later in all patients. Molecular analysis demonstrated novel missense and nonsense mutation in the patients, including p.Ile 67Ser, p.Gly328Arg, p.Arg191*, p.Asp352Asn, and p.Gly17Asp. After ERT, urine GAG was decreased in all patients. Skeletal involvement, corneal opacity, heart valve abnormalities and pulmonary function were not improved with ERT, but it had a better outcome on regarding joint motion and endurance. One patient underwent allogeneic bone marrow transplantation (BMT) prior to ERT, but their clinical response was not improved much after BMT. This study demonstrates clinical phenotypes and molecular analysis of the severe form of MPS VI in Korean patients.

Key words: Mucopolysaccharidosis, Mucopolysaccharidosis type VI, Recombinant human arylsulfatase B, enzyme replacement therapy

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Introductions

Mucopolysaccharidosis type VI (MPS VI) or Maroteaux–Lamy syndrome, an autosomal recessive lysosomal storage disease, is caused by the mutation of arylsulfatase B (ARSB gene), which results in the reduction or absence of N–acetyl–galactosamine–4–sulfatase (arylsulfatase B, ASB) activity. This defect causes an accumulation of dermatan sulfate (glycosaminoglycan, GAG), which affects many systems. The prevalence of this disease varies by nationality. It ranges from 1 in 5,000 live births in northeast Brazil to 1 in 2,057,529 births in Czech Republic^{1, 2)}. In Asia, one study from Taiwan reported an incidence of about 1 in 833,000 live births³⁾. The relative proportion of MPS VI to total MPS is quite high in Brazil, Portugal and Australia (18.48%, 16.12% and 10.36%, respectively) but low in Canada, Sweden and Norway (5%, 4% and 2%, respectively)⁴⁾. In Asia, the relative frequency of MPS VI is about 6% in Taiwan and 10% in Israel^{5, 6)}. In South Korea, the proportion of MPS VI to total MPS is extremely low, unpublished data from a single institute, Samsung Medical Center from 1994–2015 estimates that MPS VI account for 1.9% of total MPS (three MPS VI patients of total 156 patients with MPS).

MPS VI can be classified into three groups: the severe or infantile form, intermediate or juvenile form, and the mild or adult form^{7, 8)}. The onset of the severe form is usually before 2 or 3 years of age and presents with short stature, coarse face, corneal opacity, dysostosis multiplex, hepatosplenomegaly and kyphoscoliosis. All clinical symptoms usually progress rapidly. Restrictive lung disease and valvular heart disease are serious complications and leading causes of death in the

third decade of life⁴⁾. The intermediate form usually presents in late childhood with less severe skeletal involvement, valvular heart disease, corneal opacity and mild hepatomegaly. However, the patient can develop complications as a severe form including hip dysplasia, restrictive lung disease and carpal tunnel syndrome, but slower on progression. The adult form manifests in the second decade of life with mildly clinical symptoms, slower progression and involvement in fewer systems and presents with including corneal opacity, mild skeletal involvement, valvular heart disease and carpal tunnel syndrome. Height usually reaches the normal range, and patients can survive until the fifth decade of life^{4, 8)}. Enzyme replacement therapy (ERT) with recombinant human arylsulfatase–B (rhASB) for MPS VI has been approved since 2005 in the US 2006 in the EU, and 2008 in South Korea. ERT leads to the reduction of urine GAG and improvement of joint movement, pulmonary function, and endurance^{9, 10)}. Bone marrow transplantation (BMT) is another treatment option for MPS VI, but it is limited by the risks of treatment–related complications, such as graft–versus–host disease⁴⁾.

In this report, we present the clinical characteristics, molecular analysis, and clinical course of ERT of three Korean patients with the severe form of MPS VI.

Case Reports

1. Patient 1

A 4–year–old boy was referred to Samsung Medical Center with corneal opacity. He was the first child from non–consanguineous Korean parents and was born at 39 weeks of gestation with a birth weight of 3.4kg. His development was

normal for his age. The physical examination revealed cloudy corneas, coarse face, grade III/VI systolic murmurs, multiple joint stiffness, and kyphoscoliosis (Table 1). The skeletal survey showed calvarial thickening (Fig. 1A), short and broad long bones (Fig. 1B), proximal pointing of the metacarpal bones (Fig. 1C), irregular carpal and tarsal bones (Fig. 1C and 1D), paddle-shaped widened ribs (Fig. 1E), hip dysplasia (Fig. 1E), abnormal vertebral bodies and kyphoscoliosis (Fig. 1F).

The urine GAG (measured by a cetylpyridinium chloride [CPC] precipitation test) was 704.6 CPC unit/g creatinine (reference range [RR] <175 CPC unit/g creatinine). The ASB activity from cultured skin fibroblasts was 0.1 pmol/min mg protein (normal range 12–39 pmol/min mg protein). The mutational study of the ARSB gene from leukocytes showed novel compound heterozygous mutations: c.200T>G (p.Ile67Ser) and c.982G>A (p.Gly328Arg). Echocardiography showed mild aortic

Table 1. Clinical Phenotypes and Genotypes in Three Patients

Clinical manifestation	Patient 1	Patient 2	Patient 3
Sex	Male	Female	Female
Age at diagnosis	4	2	24
Enzyme activity (nmol/hr mg protein)	6	6	28
Urine GAG level at diagnosis (CPC unit/g cr.)	704.6 (RR <175)	unknown	unknown
Mutation	p.Ile67Ser/ p.Gly328Arg	p.Arg191*/ p.Asp352Asn	p.Gly17Asp (homozygous)
Clinical phenotype			
Coarse face	+	+	+
Short stature	+	+	+
Corneal opacity	+	+	+
Edematous optic disc	-	-	+
Hearing impairment	-	+	+
Valvular heart disease	AS,AR,MS,MR,TR	AR,MS,MR,TR,PR	AS,MR
Restrictive lung disease	+	+	+
Hepato (spleno)megaly	-	-	+
Dysostosis multiplex	+	+	+
Kyphoscoliosis	+	+	+
Joint contracture	Elbow, hip, knee	Hip, knee	Elbow, wrist, knee-
Carpal tunnel syndrome	+	+	+
Spinal cord compression	+	+	+
Age at start of ERT	6	15.8	27
Urine GAG level at initiation of ERT (CPC unit/g cr.)	375.9 (RR <175)	92.2 (RR <85)	83.7 (RR <85)
Endurance			
12 minutes of walking (m)			
Baseline	436	425.6	Not measured
Follow-up	741.15	725	Not measured
3 minutes of stair climbing (cm)			
Baseline	110	110	Not measured
Follow-up	154	142	Not measured
Surgery	Kyphoscoliosis and flexion deformities of tibia and ankle corrections	keratoplasty	-



Fig. 1. Radiological findings in all patients. A–F: Skeletal survey of patient 1 when he was 4 years old (before ERT). A: Calvarial thickening and J-shaped sella. B: Short and broad long bones and hypoplastic distal ulnar and radius. C: Proximal pointing of metacarpal bones and irregular carpal bones. D: Irregular tarsal bones. E: Paddle-shaped widened ribs and bilateral hip dysplasia. F: Anterior beaking of vertebral bodies and kyphoscoliosis. G–K: Skeletal survey of patient 2 when she was 15 years old (before ERT). G: Calvarial thickening and J-shaped sella. H: Short and broad long bones and hypoplastic distal ulnar and radius. I: Short and board metacarpal bone and irregular carpal bone. J: Irregular tarsal bones. K: Paddle-shaped widened ribs and bilateral hip dysplasia. L: T–L spine lateral view of patient 2 demonstrated inferior beaking and multiple collapsed vertebral bodies. M: MRI brain of patient 2 when she was 15 years old demonstrating cervicomedullary junction compression. N–O: Skeletal survey of patient 3 when she was 31 years old (after 5 years of ERT) N: Proximal pointing of metacarpal bones and irregular carpal bones. O: Paddle-shaped widened ribs. P: MRI spine of patient 3 when she was 31 years old demonstrating cervicomedullary junction compression.

stenosis (AS) and regurgitation (AR), mild mitral stenosis (MS) and regurgitation (MR) and mild tricuspid regurgitation (TR), and the ejection fraction (EF) was 68.6%. The pulmonary function test (PFT) was normal with forced vital capacity (FVC) of 109% and forced expiratory volume in one second (FEV1) of 110%.

He has received ERT with a 1 mg/kg intravenous infusion of rhASB weekly from 6 years of age. At that time, his weight and height were 17 kg (–1.4 standard deviation score [SDS]) and 107 cm (–1.8 SDS), respectively. Urine GAG rapidly declined in the first 6 months after ERT (Fig. 2). He showed no serious adverse effect except a mild transient headache that could be controlled by NSAID. He complained of decreased grip and wrist strength at 7 years. Carpal tunnel syndrome was diagnosed by electrophysiological study and he started to receive rehabilitation and occupational therapy. Range-of-motion (ROM) tests were evaluated by a goniometer¹¹⁾ and showed an improvement of the shoulder, elbow, and wrist of 10–60 degrees in all directions after 3 years of ERT (Table 2). AR progressed to moderate severity and left ventricular dilatation was found on echocardiography after 5 years of ERT, while the

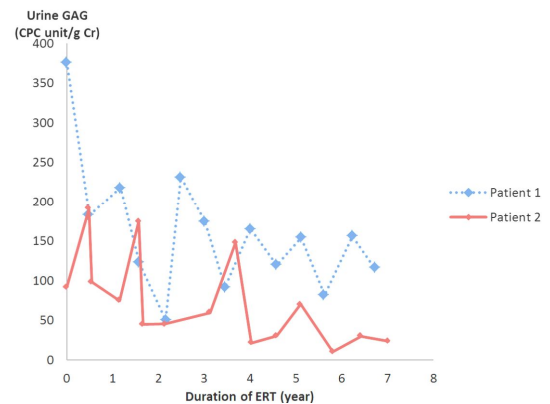


Fig. 2. Urine GAG excretion before and after ERT in patients 1 and 2.

EF was normal. PFT showed decreased FVC (79%) and FEV1 (76%) (Fig. 3), and mild restrictive lung disease developed at 10.5 years of age. His endurance was measured by a 12-minute walk test (12-MWT) and 3-minute stair climbing test (3-MSCT)^{12, 13)} at 6 and 18 months after ERT and showed improvement from 603.15 to 741.15 m in the 12-MWT and 118 to 154 cm in the 3-

MSCT (Table 1). Thoracolumbar spinal compression was found when he was 10 years old. He had back pain, difficulty to walk and had an increased deep tendon reflex. He underwent orthopedic operation for kyphosis and scoliosis correction (T10-L3) and anterior lumbar interbody fusion (T11-12 and L1-2) without any complications. After surgery, his back pain disappeared and his

Table 2. Range of Motion Tests of Patients 1 and 2 Compared before and after Treatment with ERT

Joint range of motion	Normal	Before ERT	36 months after ERT	Degree change	% change from baseline
Patient 1					
Shoulder					
Flexion (Rt/Lt)	180	100/95	150/150	50/55	50/57.9
Extension (Rt/Lt)	60	20/20	60/60	40/40	200/200
Abduction (Rt/Lt)	180	90/90	150/150	60/60	66.7/66.7
Elbow					
Flexion (Rt/Lt)	150	130/125	150/150	20/25	15.4/20
Extension (Rt/Lt)	0	flexion deformity	flexion deformity	-	-
Wrist					
Flexion (Rt/Lt)	80	60/60	70/70	10/10	16.7/16.7
Extension (Rt/Lt)	70	30/30	80/80	50/50	166.7/166.7
Hip					
Flexion (Rt/Lt)	120	120/120	120/120	-	-
Extension (Rt/Lt)	30	0/0	20/20	20/20	-
Abduction (Rt/Lt)	45	60/60	45/45	-15/-15	-25/-25
Knee					
Flexion (Rt/Lt)	135	135/135	135/135	-	-
Extension (Rt/Lt)	0	flexion deformity	flexion deformity	-	-
Patient 2					
Shoulder					
Flexion (Rt/Lt)	180	90/95	150/145	60/50	66.7/52.6
Extension (Rt/Lt)	60	20/20	40/40	20/20	100/100
Abduction (Rt/Lt)	180	70/70	110/100	40/30	57.1/42.9
Elbow					
Flexion (Rt/Lt)	150	125/125	150/150	25/25	20/20
Extension (Rt/Lt)	0	0/0	0/0	-	-
Wrist					
Flexion (Rt/Lt)	80	60/60	80/80	20/20	33.3/33.3
Extension (Rt/Lt)	70	25/25	70/70	45/45	180/180
Hip					
Flexion (Rt/Lt)	120	95/100	120/120	25/20	26.3/20
Extension (Rt/Lt)	30	flexion deformity	30/30	-	-
Abduction (Rt/Lt)	45	45/45	45/45	-	-
Knee					
Flexion (Rt/Lt)	135	105/105	135/135	30/30	28.6/28.6
Extension (Rt/Lt)	0	flexion deformity	10/10	-	-

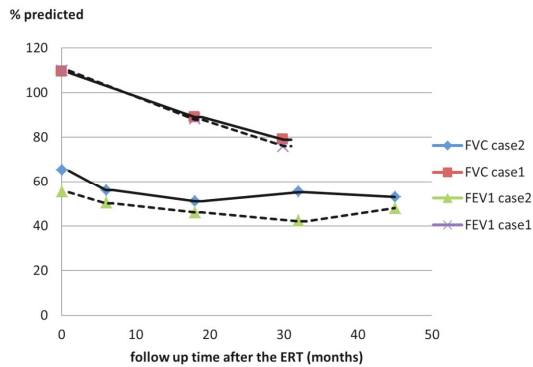


Fig. 3. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) before and after treatment with ERT of patients 1 and 2.

deep tendon reflex normalized. He received anterior and medial hemiepiphyodesis surgery for correction of the bilateral flexion and valgus deformities of the proximal tibia and ankle when he was 11 years old. The angular deformities were improved and he could walk better after correction of the angular deformities.

2. Patient 2

Patient 2 was born at full-term with a birth weight of 3 kg from non-consanguineous Korean parents. She was diagnosed with MPS VI at Soon Chun Hyang Hospital at the age of 2 years presenting with coarse face, joint stiffness, kyphosis and growth retardation. BMT was performed at 5 years of age with an HLA-matched sibling donor. After the BMT, the ASB activity in the leukocytes raised to 132.5 nmol/hr mg protein (reference range 115–226 nmol/hr mg protein). At the age of 15 years, she was referred to Samsung Medical Center for ERT. The urine GAG was 13 g/mol creatinine (reference range <5 g/mol creatinine) and the ASB activity in the leukocyte was 8.1 pmol/min protein (normal range 1.5–21). A mutational study of the ARSB gene was conducted from cultured skin fibroblasts in consideration of

post transplantation state and showed compound heterozygous mutation: c.571C>T (p.Arg191*), c.1054G>A (p.Asp352Asn). She had normal cognitive function, corneal opacity, coarse face, kyphoscoliosis, dysostosis multiplex and numbness both hands (Table 1). The skeletal survey showed calvarial thickening, J-shaped sella (Fig. 1G), short and broad long bones (Fig. 1H), irregular carpal and tarsal bones (Fig. 1I and 1J), paddle-shaped ribs, hip dysplasia (Fig. 1K), kyphosis and hypoplasia of the vertebral bodies and biconvex endplate (Fig. 1L). Magnetic resonance imaging (MRI) of the spine demonstrated cervicomedullary junction spinal compression (Fig. 1M) without any clinical symptoms. An electrophysiological study was performed due to the symptoms of numbness in both hands and the result was compatible with carpal tunnel syndrome. Echocardiography showed an EF of 68.8%, moderate AR and MR, mild MS, TR and pulmonary regurgitation (PR). PFT showed mild restrictive lung disease (FVC 65% and FEV1 55%).

ERT was started at 15.7 years of age with a weight of 20 kg (–4.2 SDS) and height of 105 cm (–10.4 SDS). The urine GAG was 92.2 CPC unit/g creatinine (reference range <85 CPC unit/g creatinine) at that time (Fig. 2). She started menarche 6 months after ERT. After three years of ERT, ROM was improved by 20–60 degrees in all directions of both shoulder, elbow, wrist, hip and knee joints (Table 2). After 5 years of ERT, MR was improved on echocardiography while the other findings were persistent. PFT showed decreased FVC and FEV1 (53% and 48%) and restrictive lung disease worsened to moderate severity after 5 years of ERT. Her endurance showed improvement by in the 12-MWT (299.4 m) and 3-MSCT (32 cm) 18 months after ERT (Table 1). The outcome of this patient was reported

several years ago¹⁴). Thereafter, cervicomedullary junction compression was followed-up by MRI at 18 years of age and the result had no change. She underwent keratoplasty of each eye at 18 and 19 years of age, respectively and the corneal grafts were been still clear after 5 years in the follow-up.

3. Patient 3

Patient 3 was born at full-term with a birth weight of 3.6 kg from non-consanguineous Korean parents. She was diagnosed with MPS VI at 24 years of age at Asan Medical Center with the following symptoms short stature, coarse face, corneal opacity, and multiple joint stiffness (Table 1). The urine GAG was 83.7 CPC unit/g creatinine (reference range <85 CPC unit/g creatinine). The ASB activity in the leukocytes was 28 nmol/hr mg protein (normal range 115–226 nmol/hr mg protein). The mutational the study of ARSB gene showed a homozygous known mutation of c.512G>A (p.Gly171Asp). Echocardiography was performed at 24 years of age and the result showed moderate AS and mild MR and was managed by bisoprolol and furosemide. The PFT was conducted at 24 years of age and the result revealed restrictive lung disease (FVC 47%, FEV1 47%).

She began ERT at Asan Medical Center at 27 years of age with a height of 127.6 cm (−6.4 SDS) and weight of 38.5 kg (−2.1 SDS). She developed weakness and radicular pain in both legs at 30 years of age that resulted in walking difficulty. However, she worked as a counselor and participated in basic activities of daily living independently. She often complained of dyspnea after running or going up stairs. She was referred to Samsung Medical Center at 31 years of age years because of foot drop and intermittent hand

weakness. The skeletal survey showed short and proximal pointing of the metacarpal bones (Fig 1N), abnormal vertebral bodies and paddle-shaped ribs (Fig. 1O). Cervical myelopathy in the cervicomedullary junction was documented by spine MRI (Fig. 1P). Her motor power was grade IV for shoulder flexion and abduction and grade V for elbow, wrist and knee flexion, ankle dorsiflexion and plantar flexion. The electrophysiological study of both median nerves was evaluated due to intermittent hand weakness, and the result showed carpal tunnel syndrome and was treated by rehabilitation and occupational therapy. She had mild stiffness of shoulder flexion and abduction (160 from 180 degrees) and wrist extension (50 from 70 degree) while the hip and knee were normal after 5.5 years of ERT. Although she was shown to have severe AS, mild MS and MR on echocardiogram, she stopped medication by herself at the age of 32 and had not been aggravated or shown chest discomfort recently. Follow-up PFT and endurance measurements were not conducted for this patient. Diffuse corneal opacity and an edematous optic disc were presented on eye examination.

Discussion

The exact prevalence of MPS VI in South Korea is unknown, but it could be very rare because only three patients have been diagnosed with MPS VI in Korea. Unpublished data from Samsung Medical Center, one of the largest MPS clinics in South Korea, from 1994–2015 shows the relative proportion of MPS VI to total MPS is only about 1.4%.

In this article, we demonstrated the clinical phenotypes of severe types of MPS VI in three Korean patients. All patients had early-onset and severe presentation including coarse face, short

stature, dysostosis multiplex, joint stiffness, valvular heart disease and cloudy corneas. Skeletal involvement is usually severe and caused short stature (−1.8 SDS in patient 1, −10.4 SDS in patient 2 and −6.4 SDS in patient 3). All patients have typical radiological findings of MPS (calvarial thickening, J-shaped sella, short and broad long bones, proximal pointing of the metacarpal bones, irregular carpal and tarsal bones, paddle-shaped widened ribs, hip dysplasia and abnormal vertebral bodies). In consequence of severe kyphoscoliosis, spinal compression and respiratory compromise developed in our patients. Although cervicomedullary junction compression is a serious complication and developed in all patients, but two patients had clinical symptoms and only one patient with clinical symptoms that were not relieved by conservative management underwent surgery. Joint stiffness was found in all patients, and the extremities were more affected than the trunk. The aortic valve is the most commonly affected among valvular heart diseases. Regurgitation is more common than stenosis pathology. Moreover, we found acquired LV dilatation in patient 1 despite normal LV function. Other common cardiac manifestations are LV hypertrophy and pulmonary hypertension¹⁵⁾, but we did not find these in our patients. Restrictive lung disease and carpal tunnel syndrome were found in all patients usually presenting later than other clinical symptoms. Hepatosplenomegaly is also a common manifestation but it was not found in patient 2 because of previous BMT. Corneal opacity usually presents early and progresses despite ERT or BMT. GAG accumulates in the donor's corneal graft and causes recurrent corneal opacity despite BMT¹⁶⁾. In our study, patient 2 underwent keratoplasty, and her corneal grafts were still clear with good visual acuity over 5 years of ERT.

More than 140 mutations in the ARSB gene have been reported. There have been a few studies on this service in Asia^{3,17–19)}. Lin et al. reported two common mutations (p.Phe399Leu and p.Leu132Pro) in Taiwan. Kantaputra et al. reported that p.Pro445Leu and p.Trp450Cys mutations were suspected to have high prevalence in India¹⁸⁾. In our study, we identified novel mutations in Korean MPS VI patients. Patient 1 had compound heterozygous mutations with 2 novel mutations: c.200T>G (p.Ile67Ser) and c.982G>A (p.Gly328Arg). Patient 2 also had compound heterozygous mutations with one novel mutation and one known mutation: c.571C>T (p.Arg191*), c.1054G>A (p.Asp352Asn). Additionally, patient 3 had a homozygous known mutation: c.512G>A (p.Gly171Asp).

ERT has been used for treatment in all patients since 2008 in South Korea. Urine GAG excretion was decreased rapidly in 6 months and then gradually decreased to a nearly normal level. The ERT was not effective for the growth and progression of kyphoscoliosis, but was effective on improvement of ROM. In this study, the ERT neither resolves nor prevents cardiac involvements as found in previous studies^{20, 21)}. Many previous studies demonstrate the improvement of PFT by ERT^{10, 20–22)}, but restrictive lung disease in our patients worsened during the ERT period. Endurance by the 12-MWT and 3-MSCT showed improvement in our study but we believe this resulted from the improvement of ROM rather than the cardiopulmonary function.

Conclusion

Mucopolysaccharidosis type VI is very rare in South Korea. This report presents the clinical features including short stature, corneal opacity, dysostosis multiplex, hepatosplenomegaly and

valvular heart disease, of three Korean patients. Three different novel mutations were identified. ERT in Korean patients has better outcomes in urine GAG excretion, joint movement and endurance. However ERT was not effective for skeletal involvement, valvular heart disease and respiratory function in this study.

요 약

뮤코다당증 6형(Mucopolysaccharidosis type VI)은 ARSB 유전자의 변이로 인하여 dermatan sulfate 대사에 관여하는 arylsulfatase B 효소의 결핍으로 유발되는 상염색체 열성 리소좀 축적 질환이다. 본 연구는 국내에서 뮤코다당증 6형으로 진단된 3명의 환자를 대상으로 하였다 3명의 환자는 최초 진단 시 뮤코다당증 6형의 특징적인 증상인 저신장, 다발성 골형성 부전, 심장 판막 이상 및 각막 혼탁을 보였으며 이후 손목 터널 증후군 및 제한성 폐질환의 양상을 보였다. 모든 환자에서 소변의 GAG (glycosaminoglycan)는 증가되어 있었으며 피부 섬유아세포 또는 백혈구에서 측정된 arylsulfatase B는 모두 감소되어 있었고 중합효소연쇄반응-염기서열분석법에 의한 ARSB 유전자 검사에서는 c.200T>G (p.Ile67Ser), c.982G>A (p.Gly328Arg), c.571C>T (p.Arg191*), c.1054G>A (p.Asp352Asn)의 이형접합체 돌연변이 및 c.512G>A (p.Gly171Asp) 동형접합체 돌연변이를 발견할 수 있었다. recombinant human Arylsulfatase B (rhASB)를 통한 효소 대체 치료는 2008년부터 국내에서도 허가되었으며 효소대체치료 시행 후 소변 GAG (glycosaminoglycan)는 감소하였으며 관절 운동 및 지구력은 향상되었다. 그러나 관절 침범 및 각막 혼탁, 심장 및 폐 침범 소견은 호전되지 않았다. 본 연구는 뮤코다당증 6형의 특징적인 증상을 보였으며 생화학적 검사 및 분자유전학적 검사를 통해 뮤코다당증 6형으로 확진된 3명의 환자를 대상으로 시행한 효소대체치료의 효과를 보고하는 바이다.

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