

Clinical Outcomes of Laminoplasty for Patients With Lysosomal Storage Disease Including Mucopolysaccharidosis and Mucopolipidoses: a Retrospective Cohort Study

Hidetomi Terai

Osaka City University: Osaka Shiritsu Daigaku

Koji Tamai (✉ koji.tamai.707@gmail.com)

Osaka City University <https://orcid.org/0000-0003-1467-2599>

Masatoshi Hoshino

Osaka City University: Osaka Shiritsu Daigaku

Hiromitsu Toyoda

Osaka City University: Osaka Shiritsu Daigaku

Akinobu Suzuki

Osaka City University: Osaka Shiritsu Daigaku

Shinji Takahashi

Osaka City University: Osaka Shiritsu Daigaku

Ysuke Hori

Osaka City University: Osaka Shiritsu Daigaku

Akito Yabu

Osaka City University: Osaka Shiritsu Daigaku

Hiroaki Nakamura

Osaka City University: Osaka Shiritsu Daigaku

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Abstract

Background:

Although the clinical efficacy of laminoplasty in adult cervical spondylotic myelopathy or ossification of posterior longitudinal ligament has been frequently reported, there are only a few reports of laminoplasty for patients with lysosome storage diseases (LSDs). Thus, this study aimed to report the midterm clinical and radiological outcomes of patients with LSDs after cervical laminoplasty.

Methods:

Six LSD patients who underwent laminoplasty with/without C1 laminectomy for cervical myelopathy were enrolled. Clinical evaluations, including the cervical Japanese Orthopedic Association (cJOA) score and visual analog scale (VAS) for upper extremity numbness and radiographic parameters, including C2-7 lordotic angle, atlanto-dens interval (ADI), and Δ ADI, were evaluated preoperatively, at 2 years postoperatively, and at the final follow-up.

Results:

Five patients had mucopolysaccharidoses (type I: n=1, II: n=3, VII: n=1) and one patient had mucopolipidoses type III. Mean age at surgery was 27.5 years. Mean postoperative follow-up period was 61 months. All mucopolysaccharidoses cases required C1 posterior arch resection with C2-C7 laminoplasty. No critical complications were observed postoperatively. There were no significant differences between preoperative and final follow-up in C2-7 angle ($p=0.724$) and Δ ADI ($p=0.592$). The cJOA score and VAS for numbness significantly improved at the final follow-up ($p=0.004$ and $p=0.007$, respectively).

Conclusion:

The cervical myelopathy of LSD patients could be safely and effectively treated with laminoplasty with/without C1 posterior arch resection after eliminating patients with atlantoaxial instability. The atlantoaxial stability and symptom improvement could be maintained at an average of 5 years postoperatively.

Background

Mucopolysaccharidoses (MPS) and mucopolipidoses (ML) are a group of rare inherited lysosomal storage diseases (LSDs). The incidence of MPS is 1.53 per 100,000 live births, although that of overall LSDs is one per 7,000¹⁻³. The accumulation of undegraded cholesterol, phospholipid, and glycosaminoglycan (GAG) substrates occurs in cell lysosomes of various tissues due to the insufficiency of metabolic enzyme. Each type of MPS and ML shows a wide spectrum of clinical manifestations, including the onset of symptoms^{4,5}. The accumulation of storage materials in prenatal chondrocytes affects the primary bone formation, which results in severe skeletal manifestations, the secondary ossification center and the

epiphyseal cartilage of growth plate, and it disturbs the normal systemic endochondral and membranous bone growth after birth, which results in various skeletal impairments, known as multiplex dysostosis including the spine⁶⁻⁸.

For the past 20 years, two main medical treatments for MPS patients had been developed and currently available in practice: hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT)⁹⁻¹¹. In HSCT, healthy donor cells are transplanted, and the enzymes secreted by donor cells are then taken up by the recipient's body through cross-correction; ERT, on the other hand, delivers the specific recombinant enzyme that is deficient in the patient. As the prognosis of the patients with LSDs is expected to be prolonged with these new therapies, the improvement of the quality of life (QOL) of such patients could be the next challenge.

Typical spinal manifestations among LSDs are atlantoaxial instability and cervical developmental spinal canal stenosis^{12,13}. Spinal disorders and its severity are different depending on disease type and activity. Atlantoaxial instability is frequently observed in MPS I, IV, and VI. Cervical stenosis is widely recognized in most type of MPS, including types I, II, VI, VII, and ML^{14,15}. Among spinal disorders, the progression of cervical canal narrowing, and its resultant cervical myelopathy are critical challenges in patients with LSDs because these directly lead to the deterioration of the patients' QOL. Thus, patients who have cervical stenosis could require surgical intervention^{13,16,17}.

Laminoplasty is the established surgical technique to treat multilevel cervical stenosis and it is widely performed for cervical spondylotic myelopathy (CSM) and ossification of posterior longitudinal ligament (OPLL)¹⁸⁻²⁰. The advantages of cervical spine laminoplasty include possible preservation of cervical range of motion (ROM) and prevention of postoperative kyphotic deformity due to the preservation of posterior elements²¹⁻²³. Although many studies have proven the clinical efficacy of laminoplasty in adult CSM or OPLL^{19,24,25}, there are only a few reports of laminoplasty for patients with LSDs. Therefore, this study aimed to report the midterm clinical and radiological outcomes of patients with LSDs after cervical laminoplasty.

Results

Demographic data of each patient including disease type, age at surgery, presence of supportive therapies, clinical scores, and follow-up period after surgery are listed in Table 1. Patients' mean age at surgery was 27.5 (13-38) years, and the mean follow-up period was 61 (30-108) months. Four out of six cases were treated with ERT. The main stenotic level in 5 out of 6 cases was C1 (Table 2).

Table 1
Demographics of the six patients with LSDs

Patient no.	Disease type	Age at surgery (years)	Sex	Medical therapy	cJOA score (points)	VAS (mm)	Follow-up (month)
#1	MLP type III	38	Female	-	12	20	72
#2	MPS type I	19	Male	ERT/ HSCT	14	70	48
#3	MPS type II	13	Male	ERT	16	60	108
#4	MPS type II	38	Male	ERT	11.5	60	48
#5	MPS type II	37	Male	ERT	12.5	10	30
#6	MPS type VII	20	Male	-	13	80	60

LSDs: lysosomal storage disease, MLP: mucopolysaccharidosis, MPS: mucopolysaccharidosis, ERT: enzyme replacement therapy, HSCT: hematopoietic stem cell transplantation, cJOA: cervical Japanese Orthopedic Association

Table 2
Preoperative radiographic characteristic of the six patients with LSDs

Patient no.	C2/7 angle (degree)	ADI (mm)	Δ ADI (mm)	ADI of CT (mm)	ROM (degree)	Most stenotic level on MRI
#1	4	1	0.1	1.3	62	C3-4
#2	4	1	0.4	1.7	53	C1
#3	16	2.5	2	2.2	56	C1
#4	-1	1.6	1.4	1.6	54	C1
#5	2	1.3	0.2	1.4	56	C1
#6	39	1.9	1	2.4	69	C1

ADI: atlanto-dens interval, ROM: range of motion

All MPS cases required C1 posterior arch resection accompanied by C2-C7 laminoplasty, while the ML case was treated with C2-C7 laminoplasty without C1 posterior arch resection. No critical complication after surgery was observed in this cohort. Cervical ROM significantly decreased from $58.3^{\circ} \pm 13.7^{\circ}$

preoperatively to $35.5^{\circ} \pm 10.7^{\circ}$ at the final follow-up ($p = 0.003$); meanwhile, the C2-7 angle preoperatively and at the final follow-up showed no significant differences ($10.7^{\circ} \pm 13.7^{\circ}$ vs. $14.0^{\circ} \pm 15.3^{\circ}$, $p = 0.724$, Table 3), as well as atlanto-dens interval (ADI) and Δ ADI (ADI: 1.6 ± 0.5 vs. 1.5 ± 0.4 , $p = 0.651$, Δ ADI: 0.9 ± 0.7 vs. 0.7 ± 0.4 , $p = 0.592$). Computer tomography (CT) scans revealed bony fusion of the gutter at 12 months postoperatively in all cases. Magnetic resonance imaging (MRI) showed that the canal expansion remained after surgery. High intensity changes on T2-weighted MRI scans were recognized in four cases (cases 1, 4, 5, and 6) before surgery, which still continued until the final follow-up. The progress of stenosis or instability caused by new accumulations or surgical traumas was not observed in any case. With respect to the change in clinical symptoms, the cervical Japanese Orthopedic Association (cJOA) score improved from 13.2 ± 1.5 preoperatively to 16.5 ± 0.8 at the final follow-up ($p = 0.004$, Table 4). The visual analog scale (VAS) scores of upper extremity numbness improved from 50.0 ± 25.8 preoperatively to 10.8 ± 10.2 at the final follow-up ($p = 0.007$)

Table 3
Postoperative radiographic change of the six patients with LSDs

Patient no.	ROM (degree)				C2-7 angle in neutral position			
	Preop	1 yr	2 yrs	FU	Preop	1 yr	2 yrs	FU
#1	62	16	26	23	4	15	11	11
#2	53	64	36	24	4	-5	-3	-3
#3	56	65	62	46	16	13	11	14
#4	54	39	34	29	-1	-12	-9	-2
#5	56	52	50	50	2	5	22	22
#6	69	46	48	41	39	23	21	42
Average	58.3 ± 13.7	47.0 ± 16.7	42.7 ± 11.9	35.5 ± 10.7	10.7 ± 13.7	6.5 ± 12.0	8.8 ± 11.5	14.0 ± 15.3
p-value				0.003				0.724
Patient no.	ADI (mm)				ΔADI (mm)			
	Preop	1 yr	2 yrs	FU	Preop	1 yr	2 yrs	FU
#1	1	1	1	1	0.1	0	1	0.5
#2	1	1.5	1.5	1.5	0.4	0.5	0.5	0.5
#3	2.5	1.9	1.8	2	2	0.2	1.5	1.6
#4	1.6	1.2	1.5	1	1.4	0.8	1.1	0.4
#5	1.3	1.3	1.8	1.8	0.2	0.6	0.7	0.7
#6	1.9	2.4	1.9	1.4	1	0.9	1.5	0.6
Average	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.3	1.5 ± 0.4	0.9 ± 0.7	0.5 ± 0.3	1.1 ± 0.4	0.7 ± 0.4
p-value				0.651				0.592
P-value was calculated as the comparison with preoperative values.								
Preop: Preoperative, yr: year, yrs: years,								

Table 4
Postoperative clinical change of the six patients with LSDs

Patient no.	cJOA score				Numbness			
	Preop	1 yr	2 yrs	FU	Preop	1 yr	2 yrs	FU
#1	12	16	17	17	20	0	0	0
#2	14	17	17	17	70	30	25	30
#3	16	17	17	17	60	20	20	15
#4	11.5	16	16	16	60	20	10	10
#5	12.5	17	17	17	10	0	0	0
#6	13	14	15	15	80	10	10	10
Average	13.2 ± 1.5	16.2 ± 1.1	16.5 ± 0.8	16.5 ± 0.8	50.0 ± 25.8	13.3 ± 11.1	10.8 ± 9.3	10.8 ± 10.2
p-value	0.004				0.007			
P-value was calculated as the comparison with preoperative values.								
Preop: preoperative, yr: year, yrs: years								

Representative cases

A 37-year-old male patient with MPS type II (case #5) underwent double-door laminoplasty combined with C1 posterior arch resection and partial resection of the dorsal wall of the foramen magnum (Fig. 1). The cJOA score improved from 12.5 to 17.

A 13-year-old male patient with MPS type II (case #3) underwent double-door laminoplasty combined with C1 posterior arch resection (Fig. 2).

A 38-year-old female patient with ML type III (case #1) underwent double-door laminoplasty from C2 to C7 (Fig. 3). Preoperative symptoms, including hand clumsiness and gait disturbance, disappeared immediately after surgery.

A 19-year-old male patient with MPS type I (case #2) underwent double-door laminoplasty combined with C1 posterior arch resection (Fig. 4). Although the symptom, mainly hand numbness, disappeared after surgery, cervical ROM significantly decreased at the final follow-up.

Discussion

To establish the surgical strategy for cervical myelopathy of patients with LSDs, the evaluation of upper cervical level could be critical. The main stenotic cervical level of the patients with MPS was C1 due to the hypoplasticity of the C1 lamina in our series; some types of LSDs are often accompanied by atlantoaxial instability^{12,13}. When atlantoaxial instability is evident, occipito-cervical fixation, rather than cervical laminoplasty, with C1 laminectomy should be indicated. Otherwise, the cervical myelopathy of patients with LSDs could be safely treated with laminoplasty with or without C1 posterior arch resection. In addition, the current study demonstrated that the atlantoaxial stability and the improvement of symptoms could be maintained at an average of 5 years postoperatively. The spinal cord compression at the upper cervical level could affect not only the movement of the whole extremity, but also the respiratory function. As the main cause of death of MPS is respiratory dysfunction, we strongly recommend surgically treating patients with LSDs at an earlier stage of myelopathy, such as only numbness as a symptom of myelopathy.

Regarding the surgical method of laminoplasty, open-door and double-door laminoplasties are two major methods^{26,27}. The distinct features of LSDs from those of adult CSM/OPLL include the small characteristic shape of the spine, presence of accumulation in the extradural space, and non-requirement of extradural resection of the accumulation. Based on our institution's surgical strategy, open-door laminoplasty is employed to treat adult patients with CSM/OPLL owing to sufficient space available for spacers. However, for patients with LSDs, it is challenging to put spacers and treat extradural materials with one-side opening of the laminae due to the hypertrophic deformity of the laminae (Fig. 1). In addition, age could be an important factor for selecting the surgical method. We excluded two patients, a 3-year-old boy with MPS II and a 1-year-old girl with ML type III, who underwent total laminectomy of the cervical spine from the current series, as their spines were too small to undergo laminoplasty.

One of the advantages of laminoplasty is ROM preservation and kyphotic change prevention. In this series, the postoperative cervical ROM was significantly decreased compared with the preoperative ROM, which is in accordance with the previous report analyzing patients with adult CSM/OPLL²¹⁻²³. However, in our series, the cervical ROM at an average of 5 years postoperatively was still 36° on average. As the cervical ROM is one of important factors for achieving a high QOL and for preventing dysphagia²⁸, we recommend avoiding fusion surgery as much as possible. In addition, although patients with LSDs still have a much shorter life expectancy than the normal population, it could be prolonged owing to the development of patient care and interventions, such as ERT and HSCT⁹⁻¹¹. The prolonged life induces degenerative changes in the joint and spine, which may require additional surgical interventions. It is now significant to consider and introduce surgical methods that can prevent degenerative changes, such as adjacent disc degeneration observed after an ordinal spine surgery.

Another advantage of cervical laminoplasty compared with cervical laminectomy is the low incidence of kyphotic change postoperatively. Machino et al. reported that nearly 8% of patients are predisposed to cervical kyphosis²⁹. Moreover, McGirt et al. reported that laminoplasty for the resection of intramedullary spinal cord tumor in children was associated with a decreased incidence of progressive spinal deformity

requiring fusion compared with laminectomy³⁰. In accordance with such studies, current results showed no significant change in the C2-7 angle at an average of 5 years postoperatively.

The disadvantage of the cervical laminoplasty is the limited indication for pediatric patients with LSDs, as their laminar size is too small to undergo laminoplasty and to allow placement of a spacer. In addition, although there are some types of spacers for cervical laminoplasty, all of them were designed for adult patients, and no spacers that could fit small pediatric patients were noted. Indeed, during the study period, we have two patients in whom laminectomy was performed, rather than laminoplasty, owing to the small laminae.

Several limitations to the present study need to be addressed. Firstly, the retrospective nature of the study makes it difficult to exclude bias, especially regarding the referral for a certain postoperative rehabilitation program and the particular surgical techniques utilized. Secondly, the number of patients is relatively small and the disease type is inconsistent. In addition, this study is a case series, not a comparative study. All these limitations prevent us from making a definitive conclusion regarding the safety and clinical outcomes of surgical treatment for patients with LSDs. However, the possibility for spine physicians to treat such patients is significantly increasing owing to the current advancement in medical treatment. Therefore, we believe that our data could be useful for spine physicians when treating cervical myelopathy in patients with LSDs.

Conclusion

In the current case series, we found that the cervical myelopathy of patients with LSDs could be safely treated with laminoplasty with or without C1 posterior arch resection after eliminating patients with atlantoaxial instability. Additionally, the current study confirmed that the atlantoaxial stability and improvement of symptoms could be maintained at an average of 5 years postoperatively.

Material And Methods

Study design and ethics

We conducted a retrospective cohort study. All study participants provided an informed consent and written consent was obtained from all of them. The study protocol was approved by the Institutional Review Board of our institution (No. 3170). No funds were received in support of this work. No benefits in any form have been or will be received from a commercial party directly or indirectly related to the subject of this manuscript. All procedures were performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Patient population

From December 2011 to March 2018, six patients with MPS (type I: 1, II: 3, VII: 1) or MLS type III underwent laminoplasty with or without C1 laminectomy for cervical myelopathy by a single surgeon in

our orthopedic surgery department. All patients underwent MRI, CT, and dynamic cervical radiography preoperatively to evaluate the level of stenosis and segmental instability. One patient with atlantoaxial instability, defined as an ADI of > 3 mm measured on preoperative neutral radiography or CT images, was treated with fusion surgery and excluded from the current case series. Moreover, two patients aged ≥ 3 years were excluded as their laminae were too small to undergo laminoplasty; thus, they were treated with laminectomy instead. General conditions and airway status were carefully evaluated by a pediatrician and an anesthesiologist prior to the induction of general anesthesia. All patients required fiberoptic intubation due to airway management difficulty related to the narrowing of oropharynx and airway or trismus.

Surgical technique

Patients were carefully positioned prone while keeping the neck on a neutral position after the head was fixed with a MAYFIELD fixator. Skull bone thickness was checked by CT scan before the MAYFIELD fixator was applied. For patients aged < 10 years or those with a thin skull, we used a halo vest instead of using the MAYFIELD fixator³¹. Intraoperative neurophysiological monitoring is recommended for the spinal surgery of LSDs³². A midline incision from the occipital to the T1 lamina process is created and paraspinal muscles, including the semispinalis, are detached with a tiny bone chip and exposed laterally from the laminae. A midline cut is made; then, gutters are made on both sides inside the facet joint to leave a thin inner cortex to make hinges using a high-speed drill. This process is completed from C2 to C7. The dorsal wall of the foramen magnum is partially resected as necessary. As for C1, the posterior arch is resected until the lateral edge of the dura mater is visualized followed by the subtotal resection of the atlanto-occipital membrane. The LSD-related accumulated materials are located in the extra-dural space between the dura mater and yellow ligaments. Hard and elastic accumulated materials located on the dura mater should be carefully resected and removed to achieve adequate decompression. Durotomy or duroplasty is not required because the accumulation was outside of the dura mater, although they are recommended in previous reports^{31,33}. After the confirmation of dural pulsation, hydroxy apatite spacers are set to bridge the opened laminae on both sides. A drainage tube is placed after a repeated saline irrigation. Postoperative care includes obligatory intensive care monitoring because of the high risk of respiratory/cardiac insufficiency in LSDs. Patients are mobilized freely without a brace because their neck lengths are too short to make adequate cervical collars. Patients are followed up clinically with MRI and functional cervical radiography.

Clinical evaluation

Clinical evaluations were performed preoperatively, at 3 months, 1 year, and 2 years postoperatively, and at the final follow-up. The cJOA score, which is a physician-assessed score used to evaluate the severity of cervical myelopathy, was determined³⁴. The VAS for upper extremity numbness was recorded as the component of the patient-oriented score³⁵. VAS score was expressed as the value rounded off to the nearest 10.

Radiographic evaluation

Radiographic parameters were evaluated using preoperative and postoperative cervical plain radiographs. Each parameter was defined as follows: C2-C7 lordotic angle, the lordotic angle between the tangent lines of the lower endplates of C2 and lower endplates of the C7 vertebral body; ROM, defined as the difference in C2-7 lordotic angles between the maximum flexion and extension positions³⁶; ADI, the horizontal distance between the anterior arch of the atlas and the dens of the axis, and ADI was evaluated using weight-bearing radiographs at neutral, flexion, and extension positions and preoperative CT image at neutral position; and Δ ADI, the differences in ADI on weight-bearing radiographs between flexion and extension positions. Observers reviewed the images and measured the parameters using computer software (Synapse; Fujifilm, Tokyo, Japan). The bone union of the gutter was evaluated using the CT scan taken within 12 months postoperatively, and the signal change of the spinal cord was evaluated using T2-weighted images of preoperative and postoperative MRI³⁷.

Statistical analysis

Average values were presented as average \pm 1.0 standard deviation or range from minimum to maximum values. The values of the continuous variables, such as ROM, C2-7 angle, ADI, and Δ ADI, obtained preoperatively and at the final follow-up were compared using a paired t-test. In addition, the cJOA and VAS scores of upper extremity numbness obtained preoperatively and at the final follow-up were compared using a paired t-test. All analyses were performed using SPSS software (version 23; SPSS, Chicago, IL). A p-value < 0.05 was considered statistically significant.

Abbreviations

ADI atlanto-dens interval

cJOA cervical Japanese Orthopedic Association

CSM cervical spondylotic myelopathy

CT computer tomography

ERT enzyme replacement therapy

GAG glycosaminoglycan

HSCT hematopoietic stem cell transplantation

LSDs lysosome storage diseases

ML mucopolidoses

MPS Mucopolysaccharidoses

MRI Magnetic Resonance Imaging

OPLL ossification of posterior longitudinal ligament

QOL quality of life

ROM range of motion

VAS visual analog scale

Declarations

Declarations: All study participants provided an informed consent and written consent was obtained from all of them.

Ethics approval and consent to participate: The study protocol was approved by the Institutional Review Board of our institution (No. 3170). All procedures were performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. All patients provided an informed consent prior to study participation.

Consent for publication: All study participants provided an informed consent and written consent was obtained from all of them.

Availability of data and material: The datasets generated and/or analyzed in the current study are available from the corresponding author on reasonable request.

Competing interest: Nothing to disclose.

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Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by H.T., K.T., M.H., and S.T. The first draft of the manuscript was written by H.T. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure1

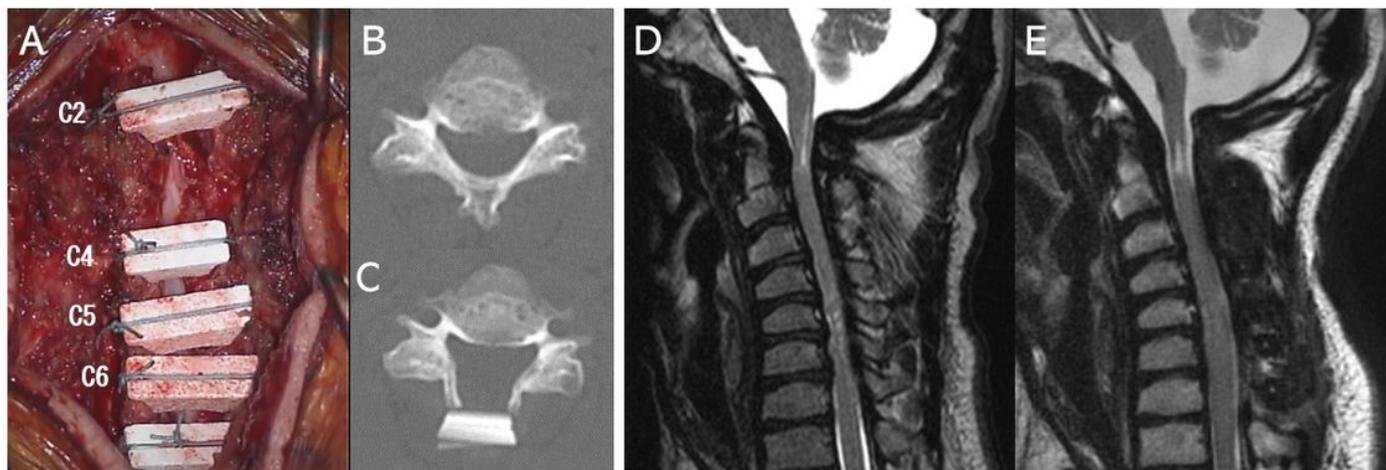


Figure 1

A 37-year-old male patient with MPS type II. Double door laminoplasty combined with C1 posterior arch resection and partial resection of dorsal wall of the foramen magnum. A: HA spacers were placed and ligated between the opened laminae. B: Axial CT image of the lamina before operation. C: Opened laminar and HA spacer (same level as B). D: T2WI MR image of the cervical spine before operation. E: T2WI MR image of the same patient at 6 months after surgery. Note that the cervical spinal canal was expanded. The high intensity area at the C1/2 level became more evident and that at the C5/6 level disappeared after surgery. MPS, mucopolysaccharidoses; HA, hydroxyapatite; CT, computed tomography; MR, magnetic resonance

Figure2

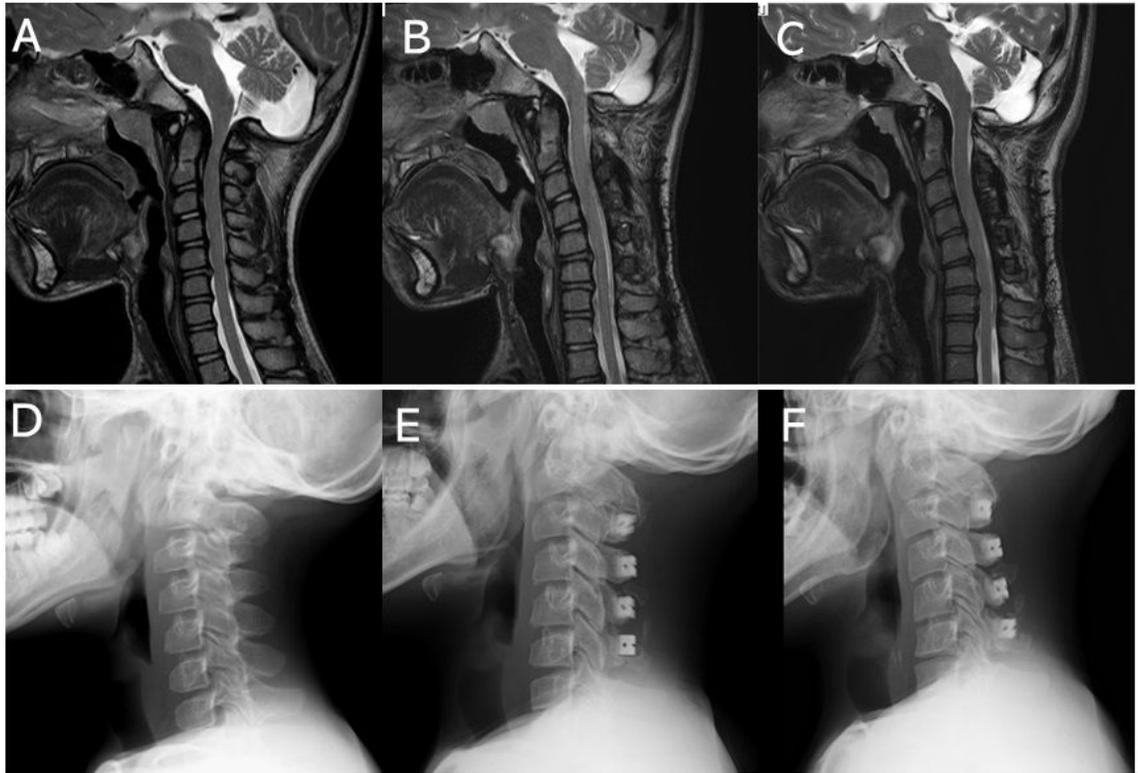


Figure 2

T2WI sagittal images and plain lateral radiographs of a 13-year-old male patient with MPS type II. The patient experienced bilateral hand numbness when his neck was extended. A, D: Before operation. B, E: Two years postoperatively. C, F: Eight years postoperatively. Symptom disappeared postoperatively. Note that the cervical kyphosis gradually progresses in 8 years without clinical symptom exacerbation. MPS, mucopolysaccharidoses

Figure3

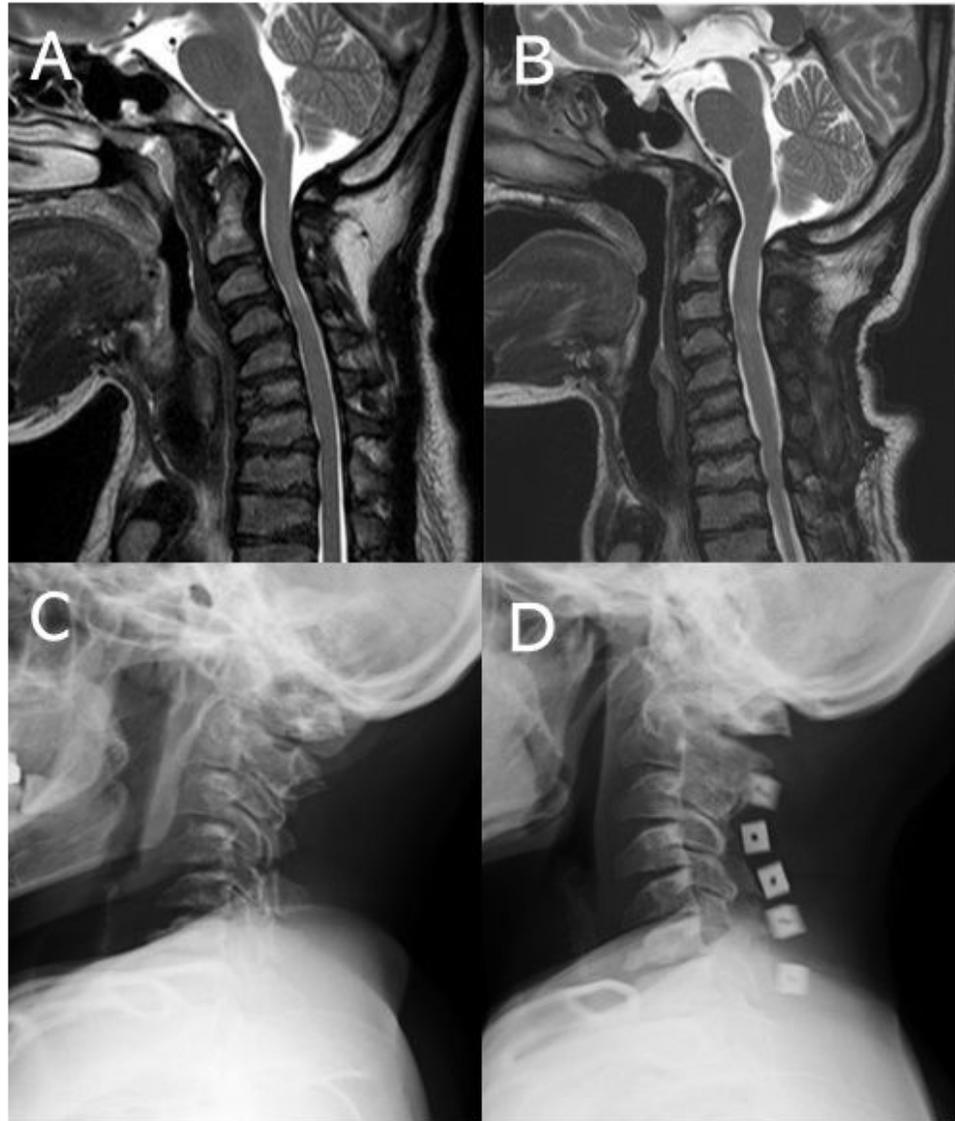


Figure 3

T2WI sagittal images and plain lateral radiographs of a 38-year-old female patient with ML type III. Her symptoms include clumsiness and gait disturbance. A, C: Before operation. B, D: Two years postoperatively. The sagittal cervical alignment became lordotic after surgery, which was maintained until the final follow-up (6 years postoperatively). Her myelopathic symptom disappeared immediately after surgery. ML, mucopolysaccharidosis

Figure4

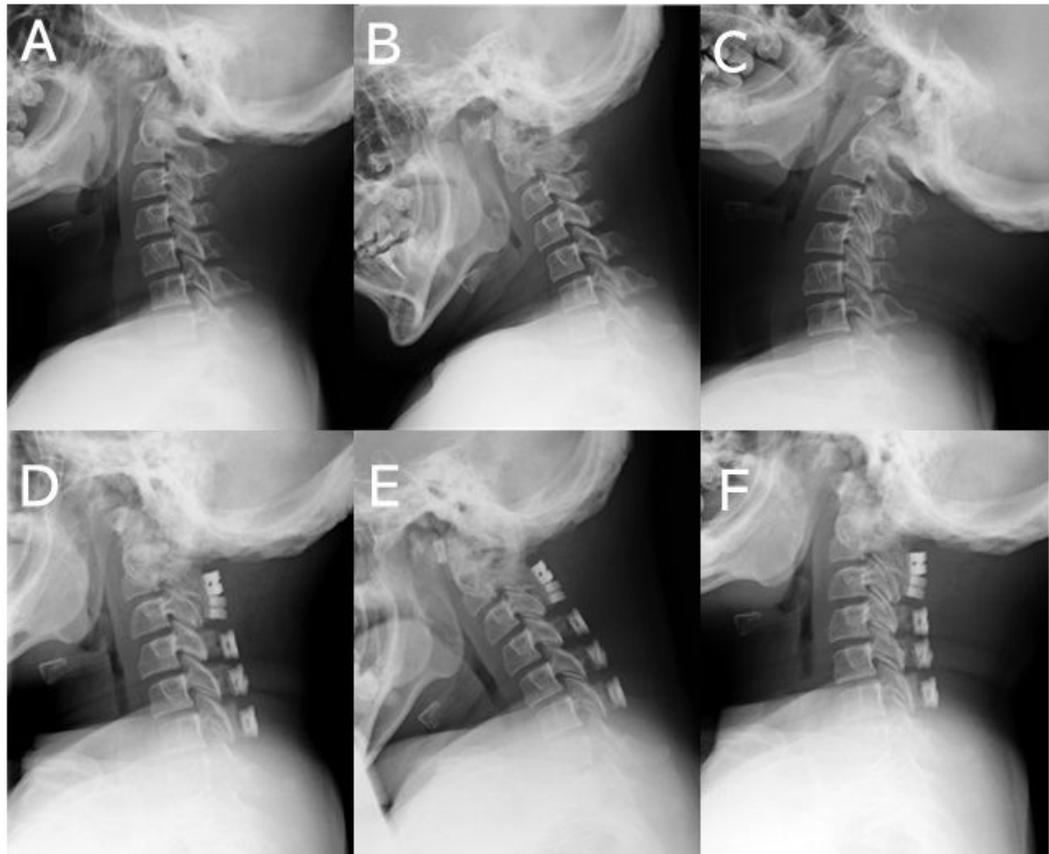


Figure 4

The cervical spine ROM after laminoplasty in a 19-year-old male patient with MPS type I. A, B, C: Plain radiographs of the cervical spine before surgery at neutral, flexion (34°), and extension (20°) positions from the left. D, E, F: Plain radiographs of the cervical spine at 4 years postoperatively at neutral, flexion (17°), and extension (12°) positions from the left. Approximately 50% reduction of ROM was observed in this patient. MPS, mucopolysaccharidoses; ROM, range of motion