the Japanese. Although the risk allele frequency in control populations is slightly different between Caucasians (22%) and Japanese (30–34%), the OR shown by investigation of the allele frequency distribution of rs7574865, 1.27, is exactly the same as in the Caucasian populations. Also, the impact of the risk allele on susceptibility to SLE in the Japanese population was found to be similar to that obtained in the previous meta-analysis of studies of Caucasian populations (1.61) (2). These results suggest that the responsible functional variant, which remains unknown, is ancient in origin. Further independent studies using populations of other ethnicities would help to prove the hypothesis.

Autoimmune diseases are initiated by breakdown of self tolerance, and thus, they may share a common pathogenesis. Indeed, some RA susceptibility genes have been identified as common risk factors for clinically different autoimmune phenotypes. One of them is *PTPN22*, which has been reported as a disease susceptibility gene for type 1 diabetes, autoimmune thyroid disease, lupus, Addison's disease, and juvenile idiopathic arthritis, in addition to RA (16). *CTLA4*, one of the genes associated with lupus and RA, especially in Asians, has also been suggested to be a disease-associated gene in a variety of other autoimmune diseases (19). Both *PTPN22* and *CTLA4* negatively regulate T cell activation and maintain peripheral tolerance, and T cells play a central role in the immunopathogenesis of autoimmune diseases. STAT-4 is suggested to be a key molecule in both the Th1 and Th17 lineages, and therefore may be involved in a common pathway of pathogenesis in autoimmune diseases.

It is reasonable to speculate that a variant on *STAT4* could also affect disease activity in autoimmune diseases through dysregulation of the Th1 and Th17 pathways. Although we did not find evidence of association between *STAT4* and disease activity in RA, we did observe a trend toward an effect of the risk allele on elevated levels of inflammation markers and patient's global assessment. Both the fact that glucocorticoid usage and dosage increased significantly in a stepwise manner in parallel with the number of risk alleles and the knowledge that glucocorticoid treatment significantly reduces levels of inflammation markers suggest that the polymorphism on *STAT4* might be associated with disease activity in RA. Although a trend toward an effect of risk allele on radiographic damage in the first 5 years was observed, it was not significant, similar to findings in the Korean study (3). However, while differences in other clinical variables among the genotypes were tested using DNA from 1,335 patients, the effect on radiographic severity was tested only in 163 patients, due to the unavailability of suitable radiographs in the others (20). As a result, the statistical power of the study of association with radiographic severity was rather limited. There were also other potential sources of artifacts that should be considered in interpretation of these preliminary data. A large prospective study, accounting for the genotypes of *STAT4*, is needed to definitively answer the question of its associations with clinical and laboratory features.

The functional variant in *STAT4* that is responsible for increased disease susceptibility remains unknown. Since the susceptibility haplotype is located within intron 3 of *STAT4*, it is considered to be responsible for splice variation or regulatory effects of STAT-4. However, it might be also possible that the putative functional variant could be responsible for a biologic effect on intragenic RNA or other factors. Studies to investigate the functional variant on the susceptibility haplotype remain to be performed.

In conclusion, using Japanese RA and SLE case–control series with large samples, we confirmed *STAT4* polymorphism as a common genetic risk factor for these autoimmune diseases. The strength of the association was found to be similar across major racial groups.

ACKNOWLEDGMENTS

We thank all of the DNA donors for making this study possible. We are grateful to Dr. Noriko Iikuni for assistance in preparation of the manuscript, and to Dr. Akihiko Miyatake (Miyatake Asthma Clinic, Osaka, Japan), the members of the Rotary Club of Osaka-Midosuji District 2660 Rotary International in Japan, and the staff of the BioBank Japan Project for supporting the study and collecting the clinical samples (RIKEN case–control series). We also thank Ms Kazue Tsugawa and Ms Aya Sato (University of Tokushima) for technical assistance, and Drs. Yoichiro Takata, Shunji Nakano (University of Tokushima) and Fumio Shinomiya (Mima Hospital, Tokushima, Japan) for aiding with patient recruitment (Tokushima case–control series). We are grateful to Dr. Atsuo Taniguchi, Mr. Eisuke Inoue, and other members of the Institute of Rheumatology, Tokyo Women's Medical University, for their work with the IORRA cohort.

AUTHOR CONTRIBUTIONS

Dr. Ikari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Ikari, Kochi, Inoue.

Acquisition of data. Ikari, Kochi, Yamamoto, Shimane, Nakamura, Toyama, Kawaguchi, Terai, Hara, Tomatsu, Yamanaka, Horiuchi, Tao, Yasumoto, Hamada, Yasui, Inoue, Itakura, Okamoto, Kamatani, Momohara.

Analysis and interpretation of data. Kobayashi, Ikari, Kaneko, Kochi, Mochizuki, Tsukahara, Inoue.
Manuscript preparation. Kobayashi, Ikari, Kochi, Inoue.
Statistical analysis. Kobayashi, Ikari.

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SPINE Volume 33, Number 9, pp 1034–1041

Surgical Results and Related Factors for Ossification of Posterior Longitudinal Ligament of the Thoracic Spine

A Multi-Institutional Retrospective Study

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Study Design. Retrospective multi-institutional study

Objective. To describe the surgical outcomes in patients with ossification of the posterior longitudinal ligament in the thoracic spine (T-OPLL) and to clarify factors related to the surgical outcomes.

Summary of Background Data. Detailed analyses of surgical outcomes of T-OPLL have been difficult because of the rarity of this disease.

Methods. The subjects were 154 patients with T-OPLL who were surgically treated at 34 institutions between 1998 and 2002. The surgical procedures were laminectomy in 36, laminoplasty in 51, anterior decompression *via* anterior approach in 25 and *via* posterior approach in 29, combined anterior and posterior fusion in 8, and sternum splitting approach in 5 patients. Instrumentation was conducted in 52 patients. Assessments were made on (1) The Japanese Orthopedic Association (JOA) scores (full score, 11 points), its recovery rates, (2) factors related to surgical results, and (3) complications and their consequences.

Results. (1) The mean JOA score before surgery was 4.6 ± 2.0 and, 7.1 ± 2.5 after surgery. The mean recovery rate was 36.8% ± 47.4%. (2) The recovery rate was 50% or higher in 72 patients (46.8%). Factors significantly related to this were location of the maximum ossification (T1–T4) (odds ratio, 2.43–4.17) and the use of instrumentation (odds ratio, 3.37). (3) The frequent complications were deterioration of myelopathy immediately after surgery in 18 (11.7%) and dural injury in 34 (22.1%) patients.

Conclusion. The factors significantly associated with favorable surgical results were maximum ossification located at the upper thoracic spine and use of instrumentation. T-OPLL at the nonkyphotic upper thoracic spine can be treated by laminoplasty that is relatively a safe surgical procedure for neural elements. The use of instrumentation allows correction of kyphosis or prevention of progression of kyphosis, thereby, enhancing and maintaining decompression effect, and its use should be considered with posterior decompression.

Key words: thoracic spine, ossification of posterior longitudinal ligament, surgical outcome, spinal instrumentation. **Spine 2008;33:1034–1041**

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Acknowledgement date: July 24, 2007. First revision date: October 16, 2007. Second revision date: November 28, 2007. Acceptance date: December 3, 2007.

The manuscript submitted does not contain information about medical device(s)/drug(s).

Federal funds were received in support of this work. No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Supported by a grant from the Japanese Ministry of Health, Labour and Welfare.

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Thoracic myelopathy caused by ossification of the posterior longitudinal ligament of the thoracic spine (T-OPLL) is usually progressive and responds poorly to conservative therapy, making surgery the only effective treatment option. Despite advancement in surgical techniques and tools employed for surgery of T-OPLL, favorable surgical results are not always achieved. Fujimura et al[1] investigated the surgical outcomes at a mean follow-up of 35 months after anterior decompression and fusion in 48 T-OPLL patients. They reported favorable overall results, but that the results were poorer in patients with a longer morbidity period, massive ossification, and ossification of other ligaments in association with T-OPLL. Matsuyama *et al*[2] investigated the surgical results in 21 patients with T-OPLL, and reported post-

operative deterioration of thoracic myelopathy in 5 of these 21 patients.

According to a radiologic study conducted by Ohtsuka *et al*,[3] the prevalence of T-OPLL was 0.8% in 1058 subjects from the general population in a rural town in Japan, which was significantly lower than that of 3.2% for OPLL of the cervical vertebrae. Thus, since the T-OPLL is a rather uncommon condition[3–5] and the number of patients visiting a single institute is limited, detailed analysis of operated cases has been difficult. A Research Group for Ossification of the Spinal Ligament sponsored by the Japanese Ministry of Health, Labor and Welfare and constituted by members from major Japanese institutions engaged in the treatment of spinal diseases, conducted a multi-institutional retrospective survey of patients who underwent surgery for T-OPLL. This report describes the results of the analyses conducted by this group with regards to the surgical outcomes, factors related to the surgical outcomes, and perioperative complications in patients with T-OPLL.

■ Materials and Methods

The survey pertained to T-OPLL patients who underwent surgery during the 5-year period from 1998 to 2002 at any one of the 34 institutions where the members of the research group belonged. In July 2004, questionnaires were sent to each institution by the secretary office of the present survey. Each institution was requested to fill in the questionnaire. The data were recovered by the end of December 2004, and a total of 198 operated cases were collected. The analysis was conducted on the data obtained from 154 of 198 patients who had postoperative follow-up period of at least 1 year and whose important data including their sex, age, preoperative neurologic status, surgical methods and results, and major complications were not missing.

The study group consisted of 62 males and 92 females, with a mean age of 56.8 years (range, 27–79 years). The mean follow-up period was 3.0 years (range, 1–6 years).

The items investigated were the patients' demographic data, the underlying disease, presence/absence of comorbidity, details of the history of spinal surgery, radiologic findings [x-ray, magnetic resonance imaging (MRI), and computed tomography], surgical methods and surgical results, complications, and the surgical outcomes.

The morphology of the T-OPLL, level of the ossified lesions, and the kyphosis angle of the thoracic vertebrae (T3, 4 to T12) were determined radiologically. The morphology of T-OPLL was classified as the linear type, beaked type, continuous waveform type, continuous cylindrical type, or the mixed type (composed of at least 2 of these types), according to the classification established by the research group in 1993 (Figures 1–3).[6] The thoracic vertebral levels of the maximum ossification and maximum cord compression were determined by computed tomography and MRI, and the presence/absence of an intramedullary high-intensity lesion was assessed on T2-weighted MR images.

The surgical outcomes were assessed by the Japanese Orthopedic Association (JOA) score for thoracic myelopathy (total of 11 points), which was derived from the JOA scoring system for cervical myelopathy by eliminating the motor and sensory scores for the upper extremity (Table 1). The recovery rate was calculated using the preoperative JOA score (points) and the JOA score at the follow-up, according to the following formula; Recovery rate = (JOA score at follow-up − preoperative JOA score)/(11 − preoperative JOA score) × 100 (%). The Frankel classification modified by Bradford *et al*[7] was also used for evaluation of the surgical outcomes.

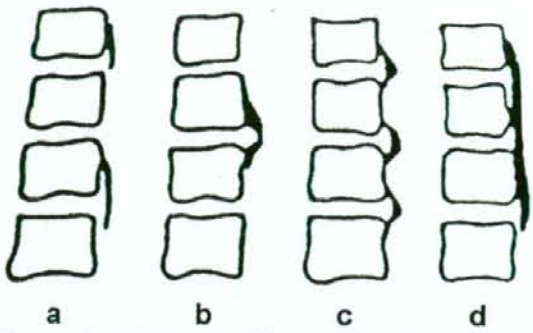

Figure 1. Classification of OPLL.[6] (**a**), linear type; (**b**) beaked type; (**c**), continuous waveform type; (**d**), continuous cylindrical type. Mixed type is defined as a combination of 2 or more different types.

Statistical Analysis

Stata 9 software (Stata Corp., College Station, TX) was used for the statistical analysis. The surgical outcomes and the factors related to the outcomes were assessed by logistic regression analysis. Age- and sex-adjusted odds ratios and their 95% confidence intervals were demonstrated.

Figure 2. Beaked type of OPLL compressing the spinal cord. Sagittal reconstruction of CAT scan of a 64-year-old man demonstrating a beaked type of OPLL.

Figure 3. Continuous cylindrical type of OPLL. Tomogram of a 48-year-old woman showing a continuous cylindrical type of OPLL.

■ Results

Clinical Data

The initial symptom was numbness of the lower extremities in 87 (56.5%), gait disturbance in 72 (46.8%), weakness of the lower extremities in 47 (30.5%), strangulating sensation of the trunk in 23 (14.9%), and urinary disturbance in 5 (3.2%) patients (some patients presented with multiple symptoms). The mean morbid period from the onset of the initial symptom to surgery was 24.3 months (range, 1–183 months). The prevalence of underlying diabetes mellitus was 22.1% (34 of 154). Twelve (7.8%) of the 154 patients had a history of decompression of the thoracic spine, and 29 (18.8%) of the 154 patients had a history of surgery in the spine other than the thoracic vertebrae; of these 29 patients, 23 had surgery for OPLL of the cervical spine, and the remaining 6 had surgery for lumbar spinal diseases (Table 2).

Table 1. JOA Scoring System for Thoracic Myelopathy

Category	Score (Point)
Motor function	
Lower extremity	
Unable to stand and walk by any means	0
Unable to walk without a cane or other support on a level	1
Walks independently on a level but needs support on stairs	2
Capable of fast but clumsy walking	3
Normal	4
Sensory function	
Lower extremity	
Apparent sensory disturbance	0
Minimal sensory disturbance	1
Normal	2
Trunk	
Apparent sensory disturbance	0
Minimal sensory disturbance	1
Normal	2
Bladder function	
Urinary retention and/or incontinence	0
Sense of retention and/or dribbling and/or thin stream and/or incomplete continence	1
Urinary retardation and/or pollakiuria	2
Normal	3

Table 2. Demographics and Clinical Data of Patients

Sex	
Male	62
Female	92
Mean age	56.8 yr (range, 27–79)
Mean follow-up	3.0 yr (range, 1–6)
Mean morbidity period	24.3 mo (range, 1–183)
Initial symptoms	
Numbness in the lower extremities	87 (56.7)
Gait disturbance	72 (46.8)
Weakness of lower extremities	47 (30.5)
Sensation of trunk strangulation	23 (14.9)
Urinary disturbance	5 (3.2)

Radiologic Findings

The morphology of T-OPLL was classified as the linear type in 8 patients (5.2%), the beaked type in 45 patients (29.2%), the continuous waveform type in 46 patients (29.9%), the continuous cylindrical type in 26 patients (16.9%), and the mixed type in 29 patients (18.8%). The level of maximum ossification was located between the first to fourth thoracic vertebrae (T1–T4) in 69 patients, T5–T8 in 62 patients, and T9–T12 in 23 patients. The mean anteroposterior diameter of the lesion at the level of the maximum ossification was 6.7 ± 2.0 mm (range, 1.5–12.0 mm). On T2-weighted MRI, an intramedullary high-intensity lesion was recognized in 83 (63.8%) of the 130 patients in whom the lesion could be evaluated. With regard to association of T-OPLL with ossification of other spinal ligaments, cervical OPLL was recognized in 97 patients (63%), and ossification of the yellow ligament in the thoracic spine was recognized in 96 patients (62.7%).

Surgical Methods. Laminectomy was conducted in 36 patients, laminoplasty in 51 patients, anterior decompression and fusion *via* an anterior extrapleural or transpleural approach in 25 patients, anterior decompression *via* a posterior approach (the method reported by Ohtsuka *et al*[8]) in 29 patients, circumferential decompression and fusion *via* a combined anterior and posterior approach reported by Tomita *et al*[9] in 8 patients, and anterior decompression and fusion *via* a sternal splitting approach in 5 patients (Table 3).[10] When the surgical procedures selected for different morphologic types of T-OPLL were assessed, the linear type was most frequently treated by laminectomy, the beaked type by

Table 3. Type of OPLL and Surgical Methods

		Type of OPLL				
	No	Linear 8 (5.2)	Beaked 45 (29.2)	Continuous Waveform 46 (29.9)	Continuous Cylindrical 26 (16.9)	Mixed 29 (18.8)
Laminectomy	36	5 (62.5)	8 (17.8)	9 (19.6)	7 (26.9)	7 (24.1)
Laminoplasty	51	0	16 (35.6)	19 (41.3)	11 (42.3)	5 (17.2)
Anterior decompression *via* anterior approach	25	0	12 (26.7)	4 (8.7)	2 (7.7)	7 (24.1)
Anterior decompression *via* posterior approach	29	3 (37.5)	5 (11.1)	12 (26.1)	6 (23.1)	3 (10.3)
Circumferential decompression	8	0	2 (4.4)	2 (4.3)	0	4 (13.8)
Sternum splitting approach	5	0	2 (4.4)	0	0	3 (10.3)

Values inside parentheses indicate percentages.

laminoplasty, and anterior decompression and fusion *via* anterior approach, the continuous waveform type and the continuous cylindrical type by laminoplasty, and the mixed type by laminectomy, and anterior decompression and fusion *via* anterior approach.

When the procedures selected for different levels of maximum ossification were assessed, laminoplasty was conducted in 50% of all patients with maximum ossification at the level of T1–T4, laminectomy, laminoplasty, and anterior decompression and fusion *via* anterior approach were conducted at almost the same frequency in patients with maximum ossification at the level of T5–T8, whereas laminectomy was conducted in 52% of all the patients with maximum ossification at the level of T9–T12 (Table 4).

Augmentation by spinal instrumentation was conducted in 52 patients (33%), posterior instrumentation in 50 patients, and anterior instrumentation in the remaining 2 patients. Instrumentation was combined with laminectomy in 52.8%, with laminoplasty in 21.6%, with anterior decompression and fusion *via* anterior approach in 20.0%, with anterior decompression *via* posterior approach in 34.5%, with circumferential decompression and fusion in 87.5%, and with sternal splitting approach in none of the patients. The ossified lesion was excised in 48 patients (31.2%), thinned and floated in 25 patients (16.2%), and left untouched in 81 patients (52.6%). Intraoperative electrophysiologic monitoring was conducted in 77 patients (50.0%), and intraoperative ultrasonography was conducted in 51 patients (33.1%). Seven patients (4.5%) underwent additional decompression during the follow-up period.

Table 4. Level of OPLL and Surgical Methods

		Level of OPLL		
	No	T1–T4 69(44.8)	T5–T8 62 (40.3)	T9–T12 23(14.9)
Laminectomy	36	6 (8.7)	18 (29.0)	12 (52.2)
Laminoplasty	51	35 (50.7)	15 (24.2)	1 (4.3)
Anterior decompression *via* anterior approach	25	4 (5.8)	16 (25.8)	5 (21.7)
Anterior decompression *via* posterior approach	29	16 (23.2)	8 (12.9)	5 (21.7)
Circumferential decompression	8	3 (4.3)	5 (8.1)	0
Sternum splitting approach	5	5 (7.2)	0	0

Values inside parentheses indicate percentages.

Surgical Outcomes. The mean JOA score was 4.6 ± 2.0 before surgery, 6.9 ± 2.4 at 1 year after surgery, 7.0 ± 2.4 points at 3 years after surgery, and 7.1 ± 2.5 points at the final follow up, with a mean recovery rate of 36.8% ± 47.4% at the final follow-up. A mean recovery rate at the follow-up was 36.9% ± 23.3% in patients treated by laminectomy, 39.9% ± 39.6% by laminoplasty, 26.6% ± 46.8% by anterior decompression *via* anterior approach, 29.7% ± 53.3% by anterior decompression *via* posterior approach, 64.1% ± 28.2% by circumferential decompression, 48.1% ± 27.2% by sternum splitting approach.

The pre- and postoperative modified Frankel classification was tabulated in Table 5. The paralysis improved by at least one grade in 107 patients (69.5%), remained unchanged in 38 patients (24.7%), and deteriorated by at least one grade in 9 patients (5.8%).

Factors Related to the Surgical Outcomes. The recovery rate was 50% or higher in 72 patients (46.8%), and factors related to the recovery rate of 50% or higher were assessed, including age, sex, preoperative morbidity period, preoperative JOA score, morphologic type of the ossified lesion, anteroposterior diameter of the ossified lesion, kyphosis angle of the thoracic vertebra, intramedullary high-intensity lesion on T2 weighted MR images, level of maximum ossification, surgical method, combined use of instrumentation, and reoperation, and presence/absence of diabetes mellitus. The cut-off value of 50% was used, because the recovery rate of 50% or

Table 5. Surgical Outcomes

		Modified Frankel Classification						
	JOA Scores	A	B	C	D1	D2	D3	E
Preop.	4.6 ± 2.0	2	8	33	40	44	24	3
Follow-up	7.1 ± 2.4	1	4	7	13	38	67	24

The recovery rate of JOA scores was 36.8% ± 47.4%.
Improvement in Frankel grade was obtained in 107 patients (69.5%).

Table 6. Factors Related to Surgical Outcomes (50% or Higher Recovery Rate of JOA Scores)

Factors	% of Patients*	Odds Ratio (95% Confidence Interval)	P
Sex			
Female	48.8	1.00	
Male	47.5	0.95 (0.49–1.83)	0.877
Age			
<49	66.7	1.00	
50–59	46.7	0.44 (0.18–1.06)	0.067
60–69	41.0	0.35 (0.13–0.91)	0.032
≥70	29.4	0.21 (0.06–0.74)	0.015
Morbidity period			
<1 yr	58.5	1.00	
1–3	50.0	0.71 (0.31–1.59)	0.400
>3	34.0	0.46 (0.19–1.07)	0.073
Preop. JOA scores			
<5	51.4	1.00	
≥5	44.9	0.75 (0.38–1.46)	0.396
Type of OPLL			
Beaked/continuous wave form	51.2	1.00	
Mixed	65.4	1.87 (0.72–4.84)	0.196
Linear	16.7	0.20 (0.02–1.86)	0.157
Continuous cylindrical	34.6	0.61 (0.23–1.59)	0.311
Anteroposterior diameter of OPLL			
<5 mm	57.9	1.00	
5–10	46.9	0.73 (0.26–2.04)	0.551
≥10	70.0	1.81 (0.33–9.88)	0.492
Kyphosis angle on MRI			
<30 degrees	48.4	1.00	
≥30	51.5	1.10 (0.54–2.24)	0.794
Level of OPLL			
T1–4	59.7	1.00 *†	
T5–8	40.0	0.41 (0.19–0.87) *†	0.020
T9–12	31.8	0.24 (0.08–0.71) *†	0.010
Surgical methods			
Anterior decompression via anterior approach/Sternum splitting approach	46.7	1.00	
Anterior decompression via posterior approach	53.6	1.20 (0.40–3.43)	0.770
Circumferential decompression	87.5	8.20 (0.84–79.98)	0.071
Laminectomy/laminoplasty	43.5	0.90 (0.35–2.07)	0.727
Use of instrumentation			
No	38.7	1.00 *†	
Yes	63.0	3.40 (1.57–7.2 *†	0.002
No. of surgeries			
Single	61.0	1.00	
Two or more	46.2	0.48 (0.14–1.69)	0.251
Diabetes mellitus			
No	47.4	1.00	
Yes	50.0	1.17 (0.53–2.60)	0.702
Intramedullary high-intensity lesion			
No	44.2	1.00	
Yes	51.8	1.40 (0.65–3.02)	0.391

Sex- and age-adjusted odds ratio and the 95% confidence interval is shown except that for sex and age.
*The numbers showing percentage of patients who obtained recovery rate of 50% or higher at the follow-up in each group.
†Statistically significant difference.

higher has been considered to be good to excellent surgical outcomes in the previous literature.[11] As a result, maximum ossification at T1–T4 [odds ratio; 1 for T1–T4 *vs.* 0.41 (95% confidence interval; 0.19–0.87, $P = 0.02$) for T5–T8 and 0.24 (0.08–0.71, $P = 0.01$) for T9–T12] and combined use of instrumentation with surgery [odds ratio; 1 for without instrumentation *vs.* 3.40 (1.57–7.2, $P = 0.002$) for with instrumentation] were associated significantly with the better outcomes (Table 6). None of the other factors was significantly related to the surgical outcome; however, the outcome tended to be favorable in patients treated by circumferential decompression and fusion and in patients with a morbidity period of less than 1 year, and in patients younger than 50 years of age.

Complications. The following perioperative complications were recognized: deterioration of thoracic myelopathy immediately after the surgery in 18 patients (11.7%); epidural hematoma in 3 patients (1.9%); dural injury resulting in cerebrospinal fluid leakage in 34 patients (22.1%); respiratory complications in 8 patients (5.2%); hoarseness in 2 patients; ileus, esophageal fistula, meningitis, myocardial infarction, and enteritis in 1 patient each.

In patients with neurologic deterioration, the grades of paralysis were Frankel A in 3 patients, B in 7, C in 4, D in 4, and surgical procedures employed were laminectomy in 3 patients (8.3%), laminoplasty in 2 (3.9%), anterior decompression *via* anterior approach in 5

(20.0%), anterior decompression and fusion *via* posterior approach in 6 (20.7%), and circumferential decompression in 2 (25.0%). In this group of patients, the ossified lesion was excised in 7 patients (*i.e.*, deterioration occurred in 14.2% of 48 patients who underwent excision), thinned and floated in 7 patients (*i.e.*, 28% of 25 patients who underwent thinning and floating), and left untouched in 4 patients (*i.e.*, 4.9% if 81 patients whose ossified lesion was left untouched). Thus, neurologic deterioration was observed more frequently in surgical procedures in which the ossified lesion was excised or thinned and floated than those in which the lesion was left untouched.

Measures against immediate neurologic deterioration were administration of steroid in 14 patients, surgical evacuation of hematoma in 2. In 12 patients (66.7%), the paralysis started to recovery in 5.6 days, on average (1–30 days), after the index surgery. The paralysis improved in 1 of 3 patients with Frankel A, 6 of 7 patients with Frankel B, 2 of 4 patients with Frankel C, and all 4 patients with Frankel D paralysis. Cerebrospinal fluid leakage was managed conservatively in 26 patients, and surgically in 8 patients.

■ Discussion

In the present study, improvement by at least one grade in the modified Frankel classification was obtained in 69.5% of the T-OPLL patients after surgical treatments, and mean recovery rate of the JOA score was 37%. Thus, moderate improvement of myelopathy was obtained after surgery in T-OPLL patients. However, compared with recovery rates of cervical OPLL reported in the literature, which ranged from 43% to 63%,[11–13] the recovery rates of T-OPLL were much lower. This is possibly attributable to the following reasons: (1) posterior decompression alone for T-OPLL is minimally effective because of kyphosis of the thoracic spine except in the upper thoracic spine where some lordosis exists; (2) the blood flow to the thoracic spinal cord is less than that to the cervical spinal cord; (3) anterior approach to the thoracic spine is more difficult than that to the cervical spine, making decompression surgery more technically demanding.

Fujimura *et al*[1,14] have identified several factors related to poor surgical results, including a long morbidity period, extensive OPLL, and ossification of other spinal ligaments. Matsuyama *et al*[2] have reported that many patients with the beaked-type of OPLL showed exacerbation of the neurologic symptoms after surgery. Tokuhashi *et al*[15] have reported that the efficacy of posterior decompression for OPLL may be poorer in patients with a large kyphosis angle on preoperative MRI. In the present survey, the factors that were found to be significantly related to the surgical outcomes were the level of maximum ossification at the upper thoracic spine and the combined use of instrumentation with decompression surgery.

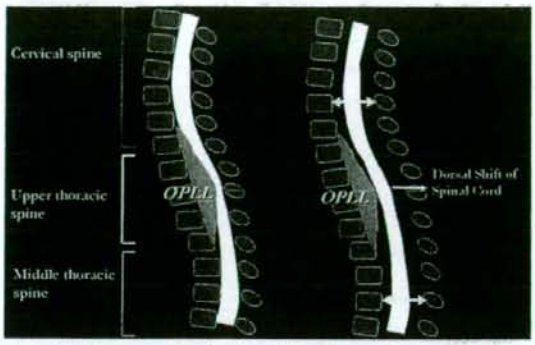

Figure 4. Schematic drawing describing the mechanism of decompression of the spinal cord by laminoplasty in patients with OPLL at the upper thoracic spine. Since the spinal curvature is usually lordotic or only slightly kyphotic at the cervicothoracic junction, dorsal shift and decompression of the spinal cord can be expected by posterior decompression alone.

Surgical method most frequently used for T-OPLL at the upper thoracic spine was laminoplasty. Since the spinal curvature is usually lordotic or only slightly kyphotic at the cervicothoracic junction, dorsal shift and decompression of the spinal cord can be expected by posterior decompression alone (Figure 4), and, therefore, T-OPLL at this level can be successfully treated by laminoplasty, which is relatively safe and is rarely associated with neurologic complications. The use of instrumentation allows correction of kyphosis or prevention of progression of kyphosis, and stabilization of the spine, thereby, enhancing and maintaining decompression effect.[16] Yamazaki *et al*[17] have reported a patient whose neurologic symptoms gradually deteriorated after laminectomy resulting in severe paraplegia. However, the patient obtained neurologic recovery after fusion with posterior instrumentation conducted 4 weeks after the initial decompression surgery. Nakanishi *et al*[18] have reported that a patient who had significant reduction of spinal evoked potential after laminectomy regained the potential level immediately after the addition of posterior instrumentation. Thus, the use of instrumentation should be considered when posterior decompression is conducted.

In the present study, there was no statistically significant difference in the surgical outcomes among patients treated by different surgical methods. Fujimura *et al*[1] and Ohtani *et al*[19] have reported that the anterior decompression is more radical and reasonable for T-OPLL in the kyphotic thoracic spine. On the other hand, Ohtsuka *et al*[8] and Tsuzuki *et al*[20] have reported that they have respectively obtained relatively favorable surgical outcomes using their posterior decompression procedures. Tomita *et al* reported the circumferential decompression method with good surgical outcomes. In the present study, although statistically not significant, the surgical outcomes of Tomita's method tended to be more favorable than those of other surgical methods. Further studies on a greater number of patients are necessary to de-

termine the differences in the clinical outcomes among various surgical procedures.

Surgery for T-OPLL was associated with a high rate of complications. Exacerbation of neurologic symptoms immediately after the surgery and cerebrospinal fluid leakage caused by dural injury were major issues of concern. Diverse explanations have been proposed to explain the neurologic deteriorations immediately after the surgery, including direct spinal cord injury during excision of the ossified lesion, progression of kyphosis after posterior decompression, epidural hematoma, *etc.* There are also cases in which no specific cause can be identified. As described earlier in this article, laminectomy alone may lead to exacerbation of paralysis in some patients, leading to the recommended use of instrumentation in conjunction with posterior decompression. When complete excision is attempted, unexpected spinal cord injury or cerebrospinal fluid leakage caused by dural injury may develop. Thinning and floating of the ossified lesion, which have been considered to be safer than complete excision, did not reduce the incidence of neurologic complications. Some attempts to make surgery for T-OPLL safer and to improve the surgical outcomes have been made, including the uses of electrophysiologic monitoring, a navigation system during excision of the ossified lesion,[21] and intraoperative ultrasonography for confirmation of decompression during posterior decompression, *etc.* Although the frequency of neurologic deterioration immediately after the surgery was as high as 11.7%, paralysis can be expected to recover spontaneously to some extent, except for the patients who developed Frankel A paralysis.

The limitations of the present study included retrospective natures of the study, the small number of patients despite the large number of participating institutions, great variations of surgical methods among institutions, all of which may make reliable statistical analysis difficult. Nonetheless, this is the largest study of surgically treated patients with T-OPLL that is a rare disease, and the results are expected to provide some guidelines for selection of the surgical treatment method in the patients with different types and levels of T-OPLL. The results may also serve as basic data for prospective studies that are planned in the near future.

■ Key Points

- Multi-institutional retrospective study of surgically treated patients with ossification of posterior longitudinal ligament in the thoracic spine was conducted.
- The mean recovery rate of Japanese Orthopedic Association Scores was 36.8% ± 47.4%.
- Factors significantly related with favorable surgical outcomes were location of the maximum ossification at the upper thoracic spine and use of spinal instrumentation.

- Multi-institutional retrospective study of 154 surgically treated patients with ossification of posterior longitudinal ligament in the thoracic spine was conducted.
- Factors significantly related with favorable surgical outcomes were location of the maximum ossification at the upper thoracic spine and the use of spinal instrumentation.
- T-OPLL at the upper thoracic spine can be treated safely by laminoplasty.
- The use of instrumentation should be considered with posterior decompression for T-OPLL at the middle and lower thoracic spine.

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J Neurosurg Spine 9:530–537, 2008

Risk factors for closure of lamina after open-door laminoplasty

Clinical article

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Object. This retrospective study was conducted to evaluate the prevalence and clinical consequences of postoperative lamina closure after open-door laminoplasty and to identify the risk factors.

Methods. Eighty-two consecutive patients with cervical myelopathy who underwent open-door laminoplasty without plates or spacers in the open side (Hirabayashi's original method) were included (62 men and 20 women with a mean age of 62 years and a mean follow-up of 1.8 years). In 67 patients the cause of cervical myelopathy was spondylotic myelopathy, and in 15 it was caused by ossification of posterior longitudinal ligament. Radiographic measurements were made of the anteroposterior diameters of the spinal canal and vertebral bodies from C3–6, and the presence of kyphosis were assessed. Lamina closure was defined as ≥ 10% decrease in the canal-to-body ratio at the final follow-up compared with that immediately after surgery at ≥ 1 vertebral level. The impact of lamina closure on neck pain, patient satisfaction, Japanese Orthopaedic Association scores, and recovery rates were also evaluated.

Results. The mean canal-to-body ratio at C3–6 was 0.69–0.72 preoperatively, 1.25–1.28 immediately after surgery, and 1.18–1.24 at the final follow-up examination. Lamina closure was observed in 34% of patients and was not associated with sex, age, or cause of myelopathy, but was significantly associated with the presence of preoperative kyphosis ($p = 0.014$). Between patients with and without lamina closure, there was no significant difference in preoperative (9.7 ± 3.1 vs 10.6 ± 2.5) and postoperative (13.7 ± 2.4 vs 13.1 ± 2.7) Japanese Orthopaedic Association scores, recovery rates ($53.9 \pm 29.9\%$ vs $44.3 \pm 29.5\%$), neck pain scores (3.5 ± 0.7 vs 3.3 ± 1.0), or patient satisfaction level (4.0 ± 1.4 vs 4.8 ± 1.0).

Conclusions. Lamina closure at ≥ 1 vertebral level occurred in 34% of patients. Although patients with lamina closure obtained equivalent recovery from myelopathy in a short-term follow-up, they tended to be less satisfied with surgery compared with those who did not have closure. The only significant risk factor identified was the presence of preoperative cervical kyphosis, and preventative methods for lamina closure, therefore, should be considered for patients with preoperative kyphosis. *(DOI: 10.3171.SPI.2008.4.08176)*

Key Words • **cervical myelopathy** • **lamina closure** • **laminoplasty**

Open-door laminoplasty was developed by Hirabayashi in 1977 and has been widely used since as a decompression method for multilevel cervical compressive myelopathy.[1,5–7,16,19] In Hirabayashi's original method, the laminae are kept open by stay sutures placed between the laminae and the muscles around the facet joint at the same level.[6,7] Although it is a simple, less time consuming and cost-effective surgical method for most patients with cervical myelopathy, it is associated with several problems including the development of postoperative axial pain,[9,10] C-5 motor palsy,[2] and closure of the opened laminae (lamina closure) among others.[21,22] Among these problems, lamina closure is a concern because it may result in suboptimal decompression of the spinal cord. Satomi et al.[21] reported that neurological deterioration due to postoperative lamina closure was observed in 2 of 51 patients with compressive cervical myelopathy who underwent a mean follow-up of 7.8 years after open-door laminoplasty. Although it has not been clarified whether postoperative lamina closure really results in suboptimal neurological recovery or causes later deterioration of cervical myelopathy, or, if so, how much

Abbreviations used in this paper: CBR = canal-to-body ratio; CI = confidence interval; JOA = Japanese Orthopaedic Association; OPLL = ossification of posterior longitudinal ligament; SD = standard deviation; VB = vertebral body.

degree of closure is clinically inacceptable, we all intuitively believe that lamina closure should be prevented.

To prevent lamina closure, several modifications to Hirabayashi's original method have been reported including the use of anchor screws adjacent to the facet joints on the hinge side,[1,15,25,27] and the use of bone grafts, spacers,[12,22] and titanium plates bridging between the laminae and the facet joints in the open side.[17,20] However, these additional procedures may increase surgical time, medical costs, risk of dislodgement and infection, and should be reserved for use in specific patients in whom these additional procedures are absolutely necessary. The purposes of this study were to evaluate the prevalence and clinical consequences of postoperative lamina closure after open-door laminoplasty and to identify its risk factors.

Methods

Eighty-two consecutive patients who underwent open-door laminoplasty for cervical myelopathy in the period between 2004 and 2005 were enrolled in this study. The patients included 62 men and 20 women with a mean age of 62.7 years (range 20–80 years). The mean follow-up period was 1.8 years (range 1–3.3 years). Sixty-seven patients had spondylotic myelopathy and 15 had OPLL. An open-door laminoplasty was used in which the lamina was dissected on the left side with a high-speed drill making the hinges on the right side. To enhance the stability of the lamina, 2.2-mm titanium anchor screws (Smith and Nephew) were placed into the facet joints on the hinge side in 68 patients (83%) who underwent treatment in the later stage of this study. The anchor screws were placed in every other level, and conventional stay sutures were used in the remaining levels. No spacer or plate was used in the open side. The day after surgery, all patients were allowed to sit up without a brace, and if possible, to stand and walk. All patients were encouraged to start range of motion exercises and isometric muscle strengthening exercise of the neck as early as possible. Therefore, all patients except those with postoperative complications followed the same clinical path after surgery.

Lateral sitting radiographs with the patient in the neutral position were obtained before surgery, immediately after surgery, at 3 months and 1 year postoperatively, and at the final follow-up. Measurements on the radiographs of the anteroposterior diameters of the VBs and spinal canal from C3–6 were made by an orthopedic surgeon (K.W.) using an electric caliper with 0.01-mm accuracy (Mitsutoyo). The kyphosis angle was defined as the angle formed by the 2 tangential lines to the posterior wall of the C-2 and C-6 VBs. To eliminate the magnifying effect of radiography, the CBR was assessed by dividing the anteroposterior diameter of the spinal canal by the diameter of the VB at each level (Fig. 1). The measurements were repeated twice and the results were averaged. To assess the intra- and interobserver reliability of measurements, radiographs obtained at the final follow-up in 25 patients were chosen in a random fashion and were measured again by the first examiner ~ 2 weeks after his first measurement and also by another orthopedic surgeon (M.M.). The intra- and interobserver reliability were

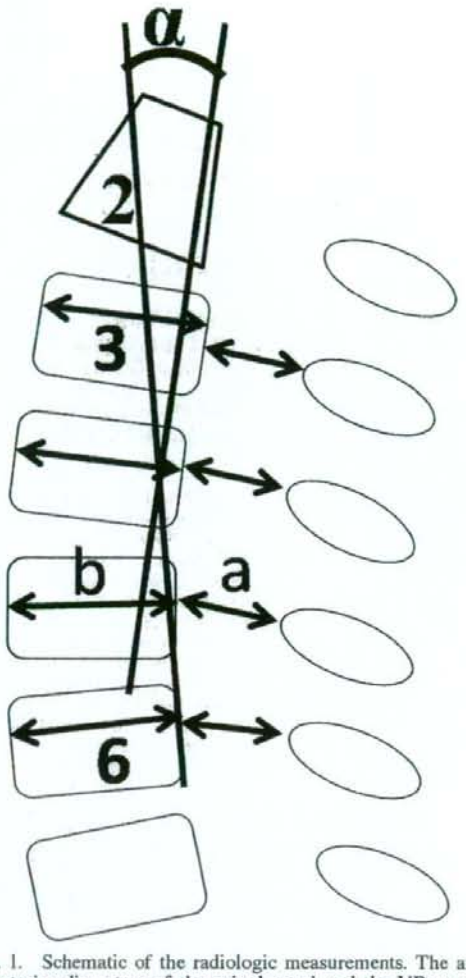

FIG. 1. Schematic of the radiologic measurements. The anteroposterior diameters of the spinal canal and the VBs were measured from C3–6. The CBR was determined by dividing the anteroposterior diameter of the spinal canal (a) by that of the VB (b). The kyphosis angle (α) was the angle formed by the 2 tangential lines to the posterior wall of the C-2 and C-6 VBs.

statistically tested using an interclass correlation coefficient. The data presented in the *Results* section are based only on the measurements obtained by the first examiner (K.W.).

Because no objective methods to evaluate lamina closure have been reported, we established a quantitative method to evaluate lamina closure. If the CBR measured immediately after surgery decreased by ≥ 10% at the final follow-up at ≥ 1 vertebral level, it was considered as lamina closure (Fig. 2). The cutoff value of a ≥ 10% decrease in CBR was determined based on the mean and range of decrease in CBR. Using radiographs of patients with lamina closure, we examined correlations between the quantitative evaluation using the CBR and conven-

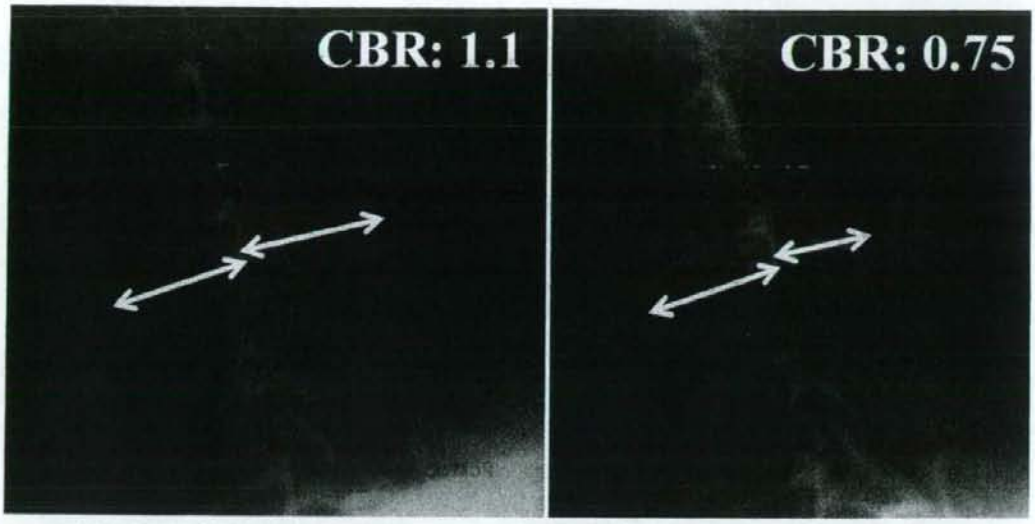

FIG. 2. Representative radiographs of lamina closure. A 32% decrease in CBR from the image obtained immediately after surgery *(left)* to the final follow-up image *(right)* is shown, indicating the presence of lamina closure.

tional qualitative evaluation, in which 2 orthopedic spine surgeons without knowledge of the results of the quantitative evaluation cooperatively made subjective judgments on whether lamina closure was present or not.

The chi-square test was used to evaluate relationships between lamina closure and factors including sex, age (< 60 or ≥ 60 years old), cause of myelopathy (spondylosis or OPLL), and the existence of preoperative cervical kyphosis.

Neurological status was evaluated using the JOA scale for cervical myelopathy (a 17-point scale),[13] and the recovery rate was calculated using the following formula established by Hirabayashi: (postoperative JOA score – preoperative JOA score) / (17 – preoperative JOA score) × 100%. Neck pain was evaluated using a 5-point scale (4 = no pain, 3 = slight pain needing no treatment, 2 = moderate pain needing occasional analgesia, 1 = pain needing a frequent analgesia, and 0 = severe pain needing daily analgesia). Patient satisfaction with surgery at follow-up was also evaluated using a 7-point grading scale (6 = very satisfied, 5 = satisfied, 4 = slightly satisfied, 3 = intermediate, 2 = slightly dissatisfied, 1 = dissatisfied, and 0 = very dissatisfied).

For statistical analyses, including the t-test, chi-square test, and Pearson and intraclass correlation coefficient, SPSS software (15.1J, SPSS Inc.) was used and probability values < 0.05 were considered statistically significant.

Results

Changes in CBR

The mean (± SD) CBRs were 0.72 ± 0.10 at C-3, 0.69 ± 0.11 at C-4, 0.71 ± 0.13 at C-5, and 0.71 ± 0.12 at C-6 before surgery; 1.25 ± 0.16 at C-3, 1.26 ± 0.11 at C-4, 1.28 ± 0.11 at C-5, and 1.27 ± 0.10 at C-6 immediately after surgery; 1.17 ± 0.10 at C-3, 1.20 ± 0.11 at C-4, 1.22 ± 0.11 at C-5, and 1.23 ± 0.10 at 1 year postoperatively; and 1.18 ± 0.10 at C-3, 1.20 ± 0.10 at C-4, 1.24 ± 0.17 at C-5, and 1.23 ± 0.10 at C-6 at the final follow-up (Fig. 3). The mean (± SD) decrease in CBR at the final follow-up compared with immediately after surgery was 5.58 ± 7.47% (range 0–52.9%) at C-3, 5.40 ± 5.13% (range 0–18.8%) at C-4, 4.93 ± 5.87% (range 0–22.6%) at C-5, and 4.83 ± 4.4% (range 0–19%). Thus, the CBRs increased significantly immediately after surgery but decreased slightly at the final follow-up at all vertebral levels. The cutoff value of a 10% decrease in CBR for determination of lamina closure was chosen because it approximately corresponded to a mean value plus a 1-SD decrease in CBR at each intervertebral level.

For intraobserver reliability of measurements, intraclass correlation coefficients for the CBR and kyphosis angle were 0.94 (95% CI 0.86–97) at C-3, 0.96 (95% CI 0.91–0.98) at C-4, 0.92 (95% CI 0.82–0.97) at C-5, 0.91 (95% CI 0.90–0.96) at C-6, and 0.99 (95% CI 0.98–0.99) for the angle of kyphosis ($p < 0.001$). Interobserver reliability was 0.83 (95% CI 0.52–0.94) at C-3, 0.85 (95% CI 0.58–0.95) at C-4, 0.90 (95% CI 0.74–0.96) at C-5, 0.85 (95% CI 0.58–0.95) at C-6, and 0.98 (95% CI 0.96–0.99) for the angle of kyphosis ($p < 0.001$). The intra- and interobserver reliability was acceptably good.

Lamina Closure

Lamina closure defined by a 10% decrease in CBR at the final follow-up was observed in 28 patients (34%). The percentage of the closed laminae per level was 25.9%

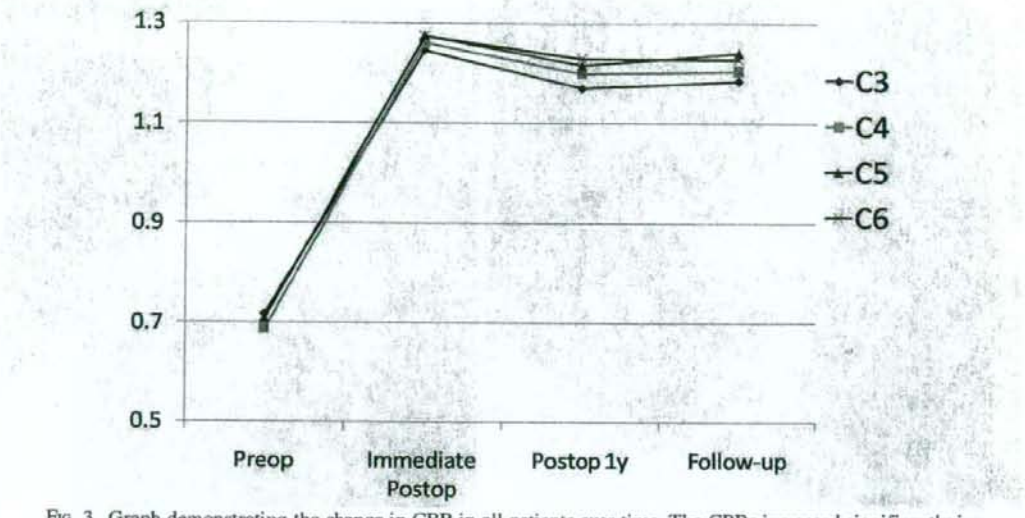

FIG. 3. Graph demonstrating the change in CBR in all patients over time. The CBRs increased significantly immediately after surgery and then decrease slightly at the final follow-up.

at C-3, 19.8% at C-4, and 23.5% at C-5, but 14.8% at C-6. The average number of closed laminae was 1.9 per patient who had lamina closure. After reading radiographs of these 28 patients, the 2 orthopedic surgeons judged that lamina closure was present in 22 of 28 patients (78.6%). When the cutoff value for lamina closure was set as a 15% decrease in CBR, 11 patients (13.4%) were identified. The orthopedic surgeons judged that lamina closure was present in 9 (81.8%) of these patients.

Chronological evaluation of CBRs in patients with lamina closure revealed that lamina closure was observed no later than 3 months after surgery at all levels (Fig. 4). Compared with patients without lamina closure, those with lamina closure demonstrated a significant decrease in CBRs at all levels ($p < 0.01$, paired t-test; Fig. 5). However, all patients with or without lamina closure had a higher CBR at follow-up than before surgery at all vertebral levels, indicating that even in cases of lamina closure, these patients obtained some decompressive effect.

Clinical Outcomes

The mean pre- and postoperative JOA scores in all patients were 10.3 ± 2.7 and 13.4 ± 2.6, respectively, and the mean recovery rate was $47.3 \pm 29.8\%$. The JOA scores

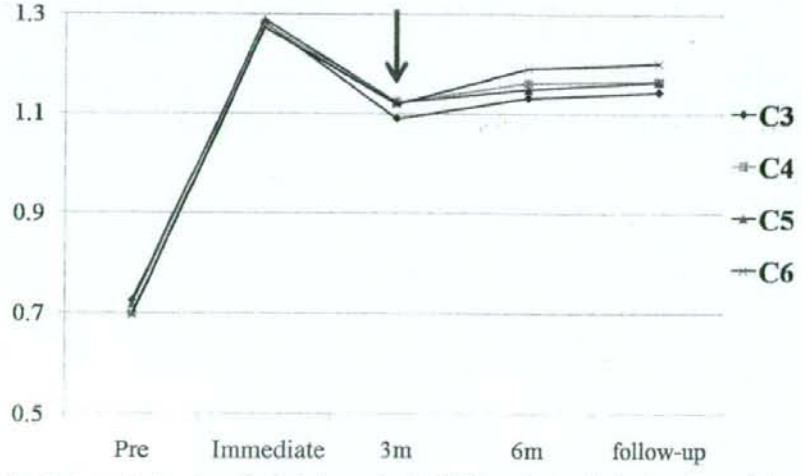

FIG. 4. Graph demonstrating chronological changes in the CBR in patients with lamina closure. A decrease in the CBRs was noted 3 months after surgery *(arrow)*.

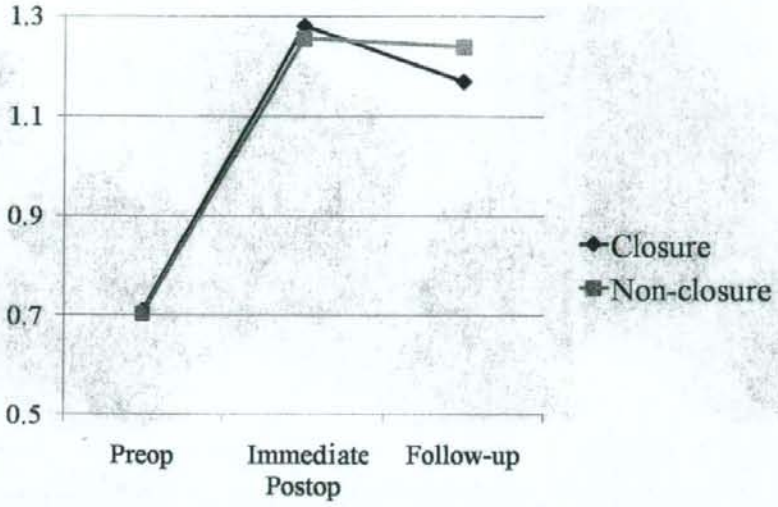

FIG. 5. Graph comparing the mean CBR between the lamina closure and nonclosure groups. The lamina closure group had a more marked decrease in mean CBR compared with the nonclosure group. The CBRs for C3–6 were averaged to obtain a mean CBR.

before surgery and at follow-up, and the recovery rates were not significantly different between the patients with lamina closure and those without (Table 1), although the patients with lamina closure tended to demonstrate a better recovery rate than those without ($p = 0.19$). There was no significant correlation between the degree of lamina closure (largest decrease in CBR at 1 of the 4 vertebral levels from C3–6) and the recovery rate (Pearson correlation coefficient = 0.29, $p = 0.80$). The patients with lamina closure were less satisfied with surgical outcomes than those without closures, although the difference was not statistically significant (mean satisfaction score 4.0 ± 1.4 for patients with closure vs 4.8 ± 1.0 for patients without; $p = 0.10$). There was no significant difference in neck pain score between the 2 groups (3.5 ± 0.7 with lamina closure vs 3.3 ± 1.0 without; $p = 0.62$).

One patient required revision surgery for a postoperative hematoma, but no patient required additional decompressive surgery for neurological deterioration secondary to lamina closure during the follow-up period of this study.

Factors Associated With Lamina Closure

Patient sex, age, cause of myelopathy, and the use of anchor screws were not significantly correlated with the occurrence of lamina closure. However, the existence of preoperative cervical kyphosis was significantly associated with lamina closure (Fig. 6). Preoperative kyphosis was observed in 14 patients (17.1%), and a mean angle of kyphosis was 13.9° (range 7–22°). Nine (64.3%) of the 14 patients with preoperative kyphosis developed postoperative lamina closure ($p = 0.014$) compared with 19 (27.9%) of 68 patients without kyphosis.

Discussion

Lamina closure has been noted as a problem associated with open-door laminoplasty. However, its prevalence and clinical consequences have not been reported in detail, partly because objective criteria for what constitutes lamina closure have not been established. In the present study, we developed the quantitative criteria assessing lamina closure in which a $\geq 10\%$ decrease in CBR at ≥ 1 level was defined as lamina closure. These criteria may be too sensitive for detection of lamina closure because there was some disagreement between the quantitative and qualitative evaluation of lamina closure. The orthopedic spine surgeons judged that lamina closure was present in only 79% of patients with a 10% decrease in CBR at the final follow-up examination. One reason for this discrepancy is that the cutoff value of 10% may be

TABLE 1

*Summary of clinical results in patients with and without lamina closure**

Parameter	Closure Group	Nonclosure Group	p Value†
JOA score			
preop	9.7 ± 3.1	10.6 ± 2.5	0.18
at final FU‡	13.7 ± 2.4	13.3 ± 2.7	0.55
recovery rate (%)	53.9 ± 29.9	44.3 ± 29.5	0.19
neck pain score	3.5 ± 0.7	3.3 ± 1.0	0.62
patient satisfaction	4.0 ± 1.4	4.8 ± 1.0	0.10

* Data are given as means ± SDs. Neck pain score and patient satisfaction scores are based on 5- and 7-point scales, respectively, and are described in *Methods*. Abbreviations: FU = follow-up; preop = preoperative.

† Unpaired t-test.

‡ Mean time to final follow-up was 1.8 years.

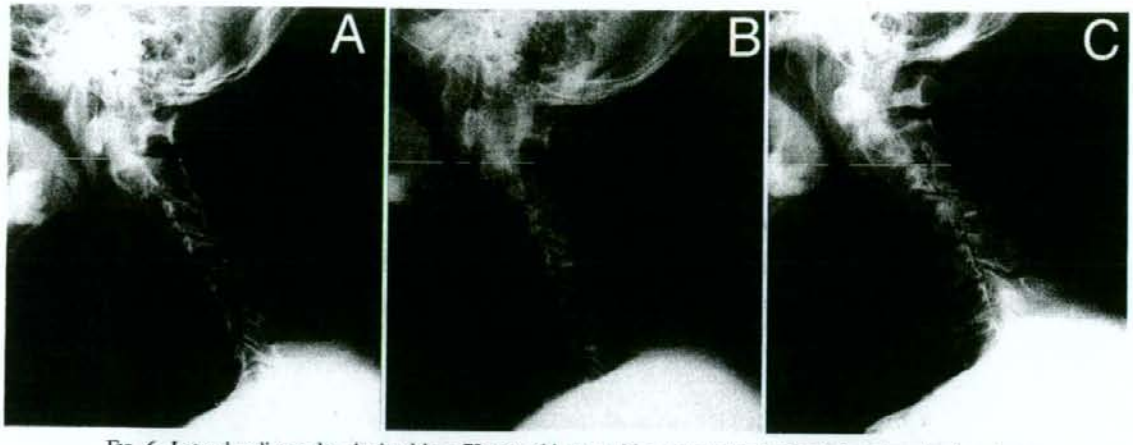

FIG. 6. Lateral radiographs obtained in a 70-year-old man with preoperative kyphosis in whom lamina closure developed despite the use of anchor screws. This patient had cervical spondylotic myelopathy with mild cervical kyphosis before surgery. The CBR of 0.81 before surgery (A) increased to 1.35 immediately after surgery (B), and decreased to 1.10 at the final follow-up examination (C). The patient obtained moderate neurological recovery (recovery rate of 48%), but was slightly dissatisfied with his surgery.

too low. However, we believe this cutoff value to be reasonable because there was no significant difference in the agreement rates of the quantitative and qualitative evaluation under the different cutoff values of 10 and 15%; 79% of patients fell within the cutoff value of 10%, and 82% were within the cutoff of 15%. Another reason for the discrepancy is that patients with a reduction in the CBR at only 1 level are also included in the lamina closure group. Nonetheless, we believe that these criteria are clinically relevant, especially now as spine surgeons try to limit the number of lamina expanded to prevent the development of postoperative axial pain.[9,24]

In the present study, lamina closure detected using the quantitative method was observed in 34% of patients. Lamina closure was observed 3 months after surgery, perhaps because the opened lamina remains unstable in the early postoperative phase. Bone formation occurs on the hinge side in the late postoperative phase, however, making the hinge stronger enough to prevent the laminae from further closure.[6,7]

Lamina closure was not related significantly to improvement in JOA scores, which tended to be better in the lamina closure group, and no patient underwent a revision surgery for neurological deterioration attributable to lamina closure. Therefore, lamina closure may not be problematic in terms of neurological recovery at least for a short postoperative period. However, patients with lamina closure tended to be less satisfied with surgery. The reason for this finding was not clear because we did not evaluate the specific reasons for the patients' satisfaction or dissatisfaction. We speculate that patients may be concerned about possible neurological deterioration in the future due to lamina closure. The inconsistency of several outcome measurements including JOA scores and patients' satisfaction may be due to the multiple factors influencing surgical outcomes, including not only lamina closure, but also presence of kyphosis, cause of myelopathy (cervical spondylosis or OPLL), patient age, and preoperative expectations for surgery.

The only risk factor for lamina closure that we identified was the presence of postoperative kyphosis. Biomechanically, the cervical spine in kyphosis is considered to have greater flexural stresses than that in lordosis.[4] In this situation, the opened laminae may be subject to more compression force by the posterior musculature, and the laminar door may be pushed forward and closed again. Although the presence of kyphosis has been known to be a factor related to unfavorable surgical outcomes after laminoplasty, and the majority of spine surgeons favor anterior surgery in patients with cervical kyphosis, several authors do not consider the presence of preoperative kyphosis in itself an absolute contraindication for laminoplasty. Chiba and colleagues[3] reported that patients with myelopathy due to cervical spondylosis were more likely than patients with OPLL to obtain a favorable neurological recovery, even with kyphosis. These authors attributed this to the redundancy of the spinal cord induced by multilevel spondylosis. Suda et al.[23] reported that patients with preoperative kyphosis < 13° can obtain moderate neurological recovery, but they found that patients with local kyphosis > 13° had poor surgical outcomes, and they recommended anterior decompression surgery or posterior correction of kyphosis for those patients. We have also indicated open-door laminoplasty to patients with mild to moderate cervical kyphosis measuring < 20°.

According to our finding that kyphosis is a risk factor for lamina closure, there is a need to use some preventative measures in addition to Hirabayashi's original method in a subset of patients with kyphosis. Because patients with kyphosis are likely to obtain less of a decompressive effect after laminoplasty compared to those without,[14] they may be more affected by lamina closure,

possibly resulting in suboptimal neurological recovery or later neurological deterioration. This is especially true of patients with OPLLs, which have a tendency to enlarge despite decompression surgery.[8,18,26] A possible solution for lamina closure is to slow the postoperative rehabilitation process. Wearing a cervical brace may be another solution. Other authors have noted however that these methods can have an adverse effect on the development of postoperative axial pain.[11] The anchor screws we used proved ineffective despite the findings of some other authors who reported their efficacy in keeping lamina opened. We therefore suggest that additional procedures such as placement of lamina spacers and plates to prevent lamina closure may be necessary in patients with cervical kyphosis. Laminoplasty may need to be avoided altogether if the kyphosis is severe (> 13° kyphotic angle).

The limitations of the present study include its retrospective nature and relatively short follow-up period. We must conduct follow-up in a cohort for a longer period of time to clarify what degree of lamina closure results in later neurological deterioration. Because our intent was to find risk factors for lamina closure, all patients followed the same postoperative clinical path. Because differences in the postoperative protocol could be a confounding factor for lamina closure, we included only patients who underwent treatment with a recently established postoperative protocol that encourages patients to stand, walk without brace, and start neck exercises as early as possible postoperatively to prevent the development of axial symptoms.

Regardless of its limitations, the present study is the first to clarify the prevalence, clinical consequences, and risk factors of lamina closure using the objective quantitative method, and provides baseline data for future long-term investigations of the relationship between clinical outcome and lamina closure.

Conclusions

Lamina closure was significantly associated with preoperative cervical kyphosis and tended to result in unfavorable patient satisfaction, although it was not significantly related to neurological recovery during the follow-up period of the study. Anchor screws were not effective in the prevention of lamina closure. In patients with preoperative cervical kyphosis, additional procedures to prevent lamina closure may be necessary, such as the placement of spacers and plates, or laminoplasty should be avoided if the kyphosis is severe.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Manuscript submitted April 29, 2008.
Accepted August 26, 2008.
A part of this work was presented at the 35th Annual Meeting of Cervical Spine Research Society at San Francisco, California, November 29 to December 1, 2007.

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J Hum Genet (2008) 53:764–768
DOI 10.1007/s10038-008-0305-z

SHORT COMMUNICATION

A compound heterozygote of novel and recurrent *DTDST* mutations results in a novel intermediate phenotype of Desbuquois dysplasia, diastrophic dysplasia, and recessive form of multiple epiphyseal dysplasia

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Received: 27 March 2008 / Accepted: 19 May 2008 / Published online: 14 June 2008

Abstract Diastrophic dysplasia sulfate transporter (DTDST) is required for synthesis of sulfated proteoglycans in cartilage, and its loss-of-function mutations result in recessively inherited chondrodysplasias. The 40 or so *DTDST* mutations reported to date cause a group of disorders termed the diastrophic dysplasia (DTD) group. The group ranges from the mildest recessive form of multiple epiphyseal dysplasia (r-MED) through the most common DTD to perinatally lethal atelosteogenesis type II and achondrogenesis 1B. Furthermore, the relationship between *DTDST* mutations, their sulfate transport function, and disease phenotypes has been described. Here we report a girl with *DTDST* mutations: a compound heterozygote of a novel p.T266I mutation and a recurrent p.ΔV340 mutation commonly found in severe phenotypes of the DTD group. In infancy, the girl presented with skeletal manifestations reminiscent of Desbuquois dysplasia, another recessively inherited chondrodysplasia, the mutations of which have never been identified. Her phenotype evolved with age into an intermediate phenotype between r-MED and DTD. Considering her clinical phenotypes and known phenotypes of p.ΔV340, p.T266I was predicted to be responsible for mild phenotypes of the DTD group. Our results further extend the phenotypic spectrum of DTDST mutations, adding Desbuquois dysplasia to the list of differential diagnosis of the DTD group.

Keywords Diastrophic dysplasia sulfate transporter (DTDST) · Diastrophic dysplasia (DTD) · Recessive form of multiple epiphyseal dysplasia (r-MED) · Desbuquois dysplasia · Genotype–phenotype correlation

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Introduction

The diastrophic dysplasia sulfate transporter gene (*DTDST*, alias *SLC26A2*) encodes membrane protein with 12 transmembrane domains composed of 739 amino acids. DTDST transports sulfate and contributes to synthesis of sulfated proteoglycans in cartilage. Approximately 40 *DTDST* mutations have been reported (Rossi and Superti-Furga 2001) in four autosomal recessive chondrodysplasias, including two nonlethal disorders, a recessive form of multiple epiphyseal dysplasia (r-MED) (Superti-Furga et al. 1999), and diastrophic dysplasia (DTD) (Hastbacka et al. 1994); and two lethal disorders, atelosteogenesis type II (AO-II) (Hastbacka et al. 1996) and achondrogenesis 1B (ACG-1B) (Superti-Furga et al. 1996a). These disorders constitute a disease spectrum termed the diastrophic

dysplasia (DTD) group (Lachman 1998; Hall 2002; Superti-Furga et al. 2007).

DTDST mutations result in reduction in either sulfate uptake or proteoglycan sulfation. In fact, chondrocytes and cartilage matrices with chondrodysplasias with *DTDST* mutations show a deficiency of intracellular sulfate and extracellular proteoglycan (Hastbacka et al. 1996; Superti-furga et al. 1996a; Rossi et al. 1997, 1998). Investigation for sulfate transporter function and cell localization of mutant DTDSTs have revealed that *DTDST* mutations are classifiable into partial-function mutations and null mutations (Karniski 2001, 2004; Maeda et al. 2006). Partial-function mutants have 39–69% sulfate transport activity compared with the wild-type DTDST (Karniski 2004). These mutant proteins are properly expressed on the cell membrane, but they are significantly less than the wild-type protein. Null mutations including p.ΔV340 create trace amounts of proteins either from poor expression or from rapid degradation. These proteins are expressed only intracellularly, not on the plasma membrane (Karniski 2004).

The genotype–phenotype correlation of *DTDST* mutations has been well described (Superti-Furga et al. 1996b; Rossi and Superti-Furga 2001; Karniski 2001, 2004). The current concept includes homozygotes for null mutations resulting in ACG-1B, heterozygotes for both null and partial-function mutations in either AO-II or DTD, and homozygotes for partial-function mutations in r-MED. However, some variants of these diseases, such as McAlister dysplasia as a variant of AO-II (Rossi et al. 1997) and broad bone platyspondyly as a variant of DTD (Mégarbané et al. 1999), have also been described. Thus, the spectrum of phenotypes caused by *DTDST* mutations may extend further.

Desbuquois dysplasia is a rare, nonlethal, autosomal recessive disease, and its causative gene was hitherto unknown. Desbuquois dysplasia is characterized by marked short stature of prenatal onset, joint laxity, round face, bulging eyes, midface hypoplasia, "Swedish-key" appearance of the proximal femora, hyperphalangy of the index finger, and advanced carpal and tarsal bone ossification (Faivre et al. 2004). The phenotypic variations are diverse, and mild Desbuquois dysplasia without hyperphalangy has been reported (Nishimura et al. 1999). The phenotype variations cause diagnostic confusion, and Desbuquois dysplasia is occasionally misdiagnosed as other chondrodysplasias such as Larsen syndrome.

Here we report an unusual phenotype in a compound heterozygote of a novel p.T266I mutation and a common p.ΔV340 mutation. The phenotype was indistinguishable in infancy from that of Desbuquois dysplasia, but it evolved into an intermediate between r-MED and DTD. Our experience raises the possibility of a novel phenotype generated by a novel *DTDST* mutation and implies difficulty in differential diagnosis between Desbuquois dysplasia and mild phenotypes in the DTD group on clinical and radiological grounds.

Materials and methods

Clinical report

The girl was born to a healthy nonconsanguineous Japanese couple by normal delivery at 40 weeks gestation. Her birth height was 49.5 cm. She had bilateral clubfeet, contracture of the MP joints, and hyperextension of bilateral knees. She also had short limbs involving all segments. The midface was somewhat flattened. Radiographs at 2 weeks of age revealed mildly broadened long bones of the legs, bilateral hip subluxation, and bilateral reduction in the talocalcaneal angles of the feet. Radiographs at 7 months of age showed broadening and Swedish-key appearance of the proximal femora and advanced carpal bone ossification (Fig. 1), which led to a diagnosis of Desbuquois dysplasia. Short stature became obvious at 3 years of age and was remarkable at 4 years of age (88 cm: −3 SD). On radiological examination at 4 years of age, our attention was drawn to proximal femoral epiphyseal dysplasia and broadening of the short tubular bones, resembling those of r-MED (Fig. 2). The findings led us to a molecular analysis of the *DTDST*.

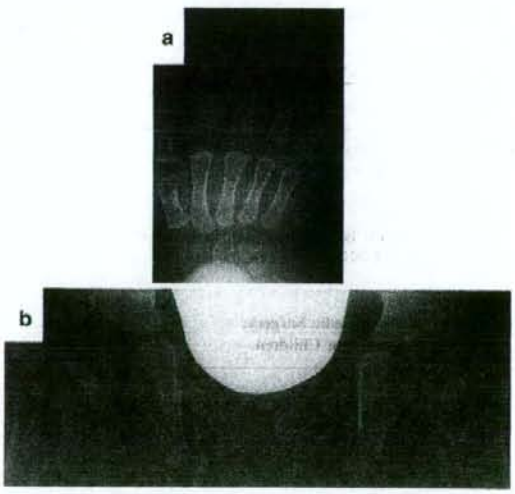

Fig. 1 X-rays at 7 months of age. **a** Metacarpal bones and phalanges were broad. Four carpal bones were visible, indicating that carpal bone ossification was advanced. **b** Swedish-key appearance of proximal femora were visible