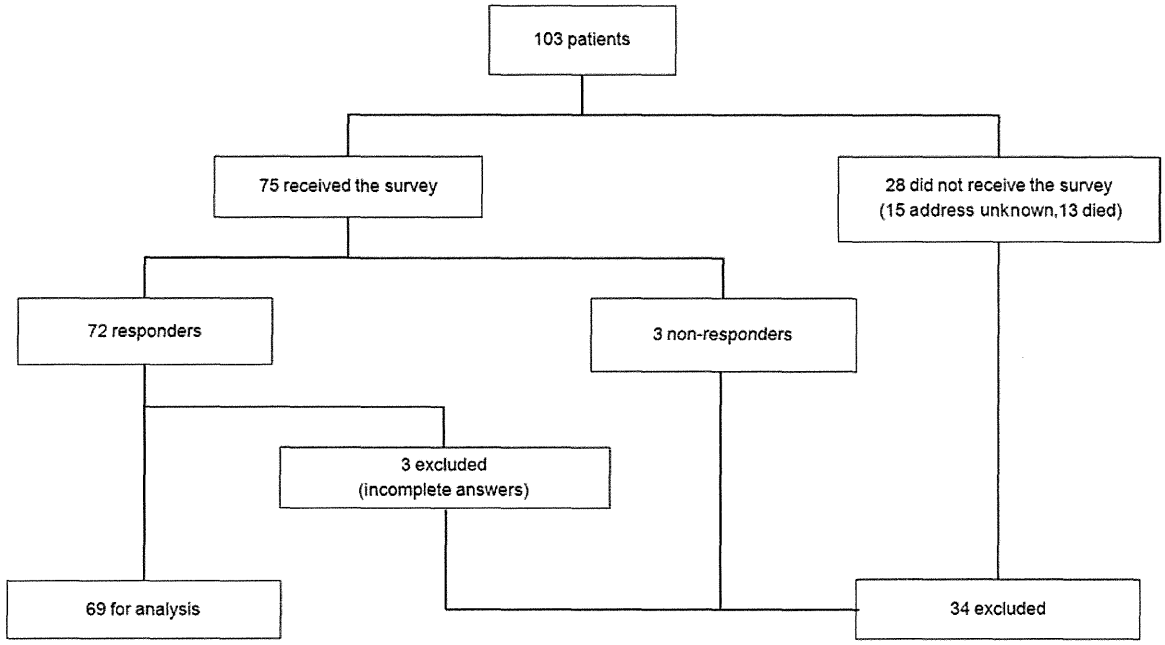

Fig. 1. Chart showing the study population. Of the 103 patients who underwent surgery and to whom the questionnaires were mailed, 69 were included in the analysis.

Patient Satisfaction

Fifty-five (80%) of the 69 participants reported being very satisfied (16%) or satisfied (64%) with the results of surgery, 7 (10%) were neither satisfied nor dissatisfied, and 7 (10%) were dissatisfied or very dissatisfied (Fig. 2). All of the patients who were very satisfied reported that their condition was very improved (13%) or improved (2.9%) by surgery. Of the satisfied patients (64%), 57% reported being very improved or improved by surgery, and 7% reported being neither improved nor worsened by surgery.

Fifty-eight patients (84%) reported that their condition was very improved or improved by surgery (Fig. 3). All of the patients who reported being very improved were very satisfied (13%) or satisfied (10%) with the results of surgery. Of the patients whose condition had improved (60.8%), 52% reported that they were very satisfied or satisfied with surgery, but 4% reported that they were neither satisfied nor dissatisfied, and the other 4% reported that they were dissatisfied with surgery.

Fifty-six patients (81%) reported that they would definitely or probably recommend surgery if family or friends suffered from the same disease (Fig. 4).

TABLE 1: Demographic data for patients included in the satisfaction study and other patients who were excluded*

Variable	Study Patients	Other Patients	p Value
no. of patients	69	34	
age at op (yrs)	57.0 ± 7.9	58.7 ± 8.4	0.3†
age at FU (yrs)	70.0 ± 8.8	72.6 ± 10.4	
sex (M/F)	49:20	25:9	1‡
no. of procedures (ACDF/lam)	23:46	7:27	0.3‡
avg range of vertebrae/laminae per op (ACDF/lam)	3:5.5	3:5.8	1‡
FU (yrs)	9.3 ± 5.0	8.2 ± 4.4	0.5†
conventional JOA score			
preop	9.8 ± 2.4	8.4 ± 3.4	0.08†
postop	13.8 ± 2.2	13.1 ± 2.4	0.09†
max	14.5 ± 1.9	13.8 ± 2.0	0.05†
postop recovery rate (%)	54.1 ± 27.1	53.4. ± 31.2	0.1†
max recovery rate (%)	65.4 ± 24.2	60.8 ± 23.7	0.3†
occupying ratio (%)	51.4 ± 14.6	46.0 ± 12.9	0.08†
complication (no. of cases)	14	4	0.4‡

* Unless otherwise indicated, values are expressed as the mean ± SD.
Abbreviations: ACDF = anterior cervical decompression and fusion; avg = average; FU = follow-up; lam = laminoplasty (posterior approach).
† According to the Mann-Whitney U-test.
‡ According to the Fisher exact probability test.

Correlation Coefficients of Satisfaction

Leg pain (rated by NRS; −0.25), QOL (based on JOACMEQ; 0.26), PF (based on SF-36; 0.33), and RP (based on SF-36; 0.25) were significantly weakly correlated with patient satisfaction. No other variables were significantly correlated with patient satisfaction. Correlates are summarized in Table 2. Of the 3 items used for assessment of pain, leg pain (rated by NRS) was strongly negatively correlated with QOL (based on JOACMEQ), and PF, RP, and bodily pain (based on SF-36).

Comparison Between the Satisfied and Dissatisfied Groups

To identify parameters related to dissatisfaction, clinical data were compared between the satisfied and dissatisfied groups (Table 3). There were no significant differences in age, sex, surgical procedure, follow-up period, complications, or depression prevalence between the 2 groups. In

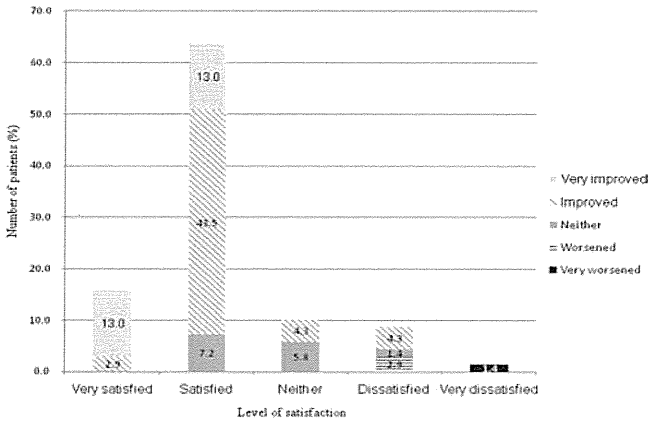

Fig. 2. Bar graph showing patient satisfaction with surgery. Eleven patients (15.9%) reported being very satisfied with the results of surgery, 44 (63.7%) were satisfied, 7 (10.1%) were neither satisfied nor dissatisfied, 6 (8.7%) were dissatisfied, and 1 (1.4%) was very dissatisfied.

patients assessed using the conventional JOA scoring system, the dissatisfied group had a significantly lower maximum score and a lower maximum recovery rate. In those assessed using the JOACMEQ, the dissatisfied group had significantly reduced LEF and QOL. In patients assessed using SF-36, the dissatisfied group showed significantly lower PF, RP, and vitality. Pain in all 3 items of the NRS was significantly more severe in the dissatisfied group than in the satisfied group. The difference in postoperative conventional JOA scores between the 2 groups was close to significant ($p = 0.05$). Reasons for dissatisfaction as recorded in responses to open-type questions are summarized in Table 4.

Logistic Regression Analysis

All parameters that were significantly correlated with satisfaction or showed significant differences between the satisfied and dissatisfied groups were entered in a stepwise logistic regression analysis model, with satisfaction as the dependent variable. Based on the results of stepwise logistic regression analysis, the following variables

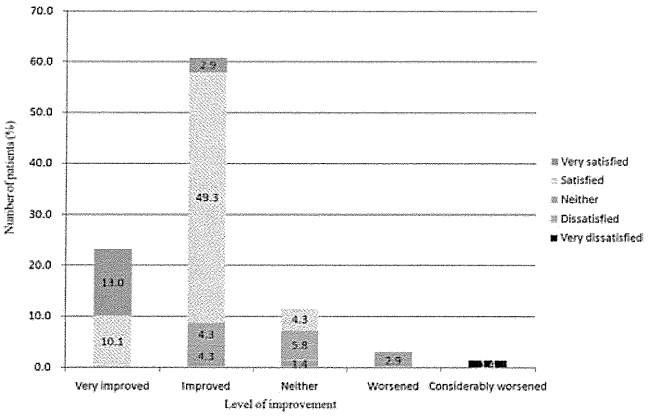

Fig. 3. Bar graph showing patients whose condition was improved by surgery. Sixteen patients (23.1%) reported being very improved by the surgery, 42 (60.8%) were improved, 8 (11.5%) were neither improved nor worsened, 2 (2.9%) were worsened, and 1 (1.4%) was considerably worsened.

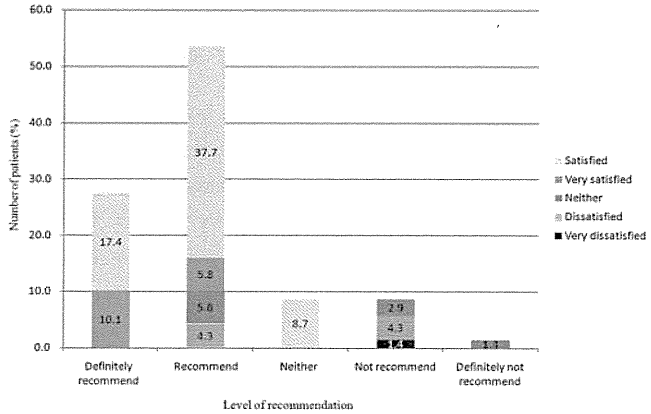

Fig. 4. Bar graph showing patients recommending surgery. Nineteen patients (27.5%) reported that they would definitely recommend the surgery, 37 (53.6%) would probably recommend the surgery, 6 (8.7%) would neither recommend nor not recommend the surgery, 6 (8.7%) would probably not recommend the surgery, and 1 (1.4%) would definitely not recommend the surgery.

were correlated with satisfaction: 1) PF (based on SF-36); 2) QOL (based on JOACMEQ); 3) LEF (based on JOACMEQ); and 4) maximum recovery rate (based on conventional JOA). The adjusted R^2 was 0.5, indicating that this model explained 50% of the variation in satisfaction as dependent (Table 5).

Discussion

To the best of our knowledge, no previous study has reported patient satisfaction with surgery for cervical OPLL that was evaluated using a patient-based method. Patient satisfaction with surgery for cervical spondylotic myelopathy has been reported to range from approximately 75% to 90%.[2,20,22] Riew et al.[20] reported an 89.8% satisfaction rate after arthroplasty for myelopathy due to single-level compression by cervical spondylosis or disc herniation in middle-aged patients. Sampath et al.[22] reported a 75% satisfaction rate after surgery for cervical myelopathy due to multilevel compression. In the present study, 80% of patients with cervical myelopathy due to multilevel compression of OPLL were satisfied with the surgical results. This positive result suggests that surgical treatment for cervical OPLL was effective according to both patient- and doctor-based evaluation. Based on statistical analysis, factors associated with satisfaction could be classified into the following general categories: QOL, PF, and improvement.

As suggested by the comparatively large Spearman rank correlation coefficient and small p value in the present study, QOL (based on JOACMEQ) was a key parameter of satisfaction. Physical function (based on SF-36) is a scale that mainly evaluates QOL and walking ability. Therefore, PF and LEF (based on JOACMEQ) are also important factors associated with satisfaction. In previous studies, as typified by the Grip and Release Test, UEF has been regarded as a representative parameter of myelopathy because it has been shown to correlate with other functional scores such as total or LEF in the conventional JOA scoring system.[19] However, in the present study, the

TABLE 2: Correlation coefficients of satisfaction in patients with cervical myelopathy due to OPLL*

	JOA Score		Recovery Rate		Pain Score (NRS)			JOACMEQ Score					SF-36 Score							
Parameter	Max	Postop	Max	Postop	Neck	Arm	Leg	CF	UEF	LEF	BF	QOL	PF	RP	BP	GH	VT	SF	RE	MH
satisfaction	0.08	0.03	0.10	0.08	−0.16	−0.15	−0.25	0.10	0.07	0.17	0.03	0.26	0.33	0.25	0.07	0.02	0.15	0.02	0.15	0.13
JOA score																				
max		0.88	0.88	0.69	−0.38	−0.38	−0.35	0.07	0.32	0.36	0.16	0.42	0.32	0.36	0.29	0.24	0.32	0.26	0.33	0.25
postop			0.77	0.78	−0.44	−0.41	0.37	0.20	0.37	0.44	0.16	0.47	0.37	0.39	0.37	0.21	0.30	0.32	0.31	0.25
recovery rate																				
max				0.83	0.41	0.32	−0.23	0.07	0.21	0.24	0.03	0.34	0.22	0.24	0.28	0.22	0.25	0.18	0.21	0.15
postop					−0.53	−0.42	−0.25	0.29	0.35	0.36	0.13	0.43	0.32	0.34	0.42	0.28	0.28	0.30	0.27	0.19
pain score (NRS)																				
neck						0.71	0.54	−0.48	−0.38	−0.34	−0.28	−0.62	−0.26	−0.38	−0.68	−0.31	−0.37	−0.26	−0.31	−0.31
arm							0.56	−0.55	−0.49	−0.35	−0.36	−0.66	−0.31	−0.47	−0.53	−0.40	−0.44	−0.35	−0.46	−0.42
leg								−0.39	−0.38	−0.43	−0.4	−0.73	−0.39	−0.49	−0.7	−0.40	−0.48	−0.34	−0.45	−0.44
JOACMEQ score																				
CF									0.62	0.43	0.44	0.44	0.38	0.44	0.49	0.43	0.39	0.40	0.40	0.35
UEF										0.75	0.45	0.58	0.59	0.58	0.48	0.42	0.44	0.61	0.59	0.48
LEF											0.46	0.63	0.76	0.68	0.45	0.33	0.49	0.66	0.69	0.57
BF												0.50	0.43	0.42	0.43	0.32	0.42	0.46	0.44	0.41
QOL													0.59	0.69	0.73	0.67	0.80	0.63	0.71	0.72
SF-36 score																				
PF														0.78	0.44	0.29	0.46	0.61	0.67	0.49
RP															0.53	0.38	0.65	0.76	0.80	0.65
BP																0.38	0.60	0.59	0.48	0.52
GH																	0.63	0.37	0.45	0.55
VT																		0.67	0.71	0.84
SF																			0.76	0.74
RE																				0.81

* BF = bladder function; BP = bodily pain; CF = cervical spine function; GH = general health; MH = mental health; RE = role emotional; SF = social functioning; VT = vitality.

TABLE 3: Comparison between satisfied and dissatisfied groups*

Parameter	Satisfied Group	Dissatisfied Group	p Value
no. of patients	55	7	
age at op (yrs)	56.4 ± 7.9	57.3 ± 6.6	0.7
age at FU (yrs)	69.3 ± 5.5	69.9 ± 7.9	
sex (M/F)	41:14	5:2	1
op procedure (ACDF/lam)	19:36	2:5	1
FU (yrs)	9.7 ± 5.1	10.4 ± 4.9	0.8
conventional JOA score			
preop	9.8 ± 2.4	9.0 ± 2.8	0.5
postop	13.8 ± 2.3	12.2 ± 2.0	0.05
max	14.6 ± 2.0	13.3 ± 1.1	0.02†
postop recovery rate (%)	55.0 ± 27.8	34.7 ± 31.2	0.1
max recovery rate (%)	67.4 ± 24.5	50.7 ± 17.5	0.03†
occupying ratio (%)	51.6 ± 14.5	51.7 ± 18.1	0.9
complication (no. of cases)	11	2	0.6
JOACMEQ score			
CF	47.5 ± 31	37.1 ± 32	0.4
UEF	76.6 ± 22.3	64.0 ± 24.3	0.2
LEF	62.5 ± 26.8	42.0 ± 20.5	0.04†
BF	71.9 ± 25.4	54.7 ± 27.7	0.1
QOL	55.7 ± 17.2	28.6 ± 13.2	0.0009†
NRS score			
neck	1.8 ± 1.6	2.9 ± 0.7	0.03†
arms	1.3 ± 1.3	2.6 ± 1.4	0.02†
legs	1.6 ± 1.5	3.7 ± 1.1	0.02†
VAS score			
neck	4.2 ± 3.1	5.3 ± 2.3	0.3
chest	1.4 ± 2.2	0.9 ± 1.4	0.5
arms or hands	3.6 ± 2.8	4.3 ± 3.3	0.6
chest to toe	3.5 ± 3.1	5.6 ± 2.9	0.08
SF-36 score			
PF	60.3 ± 28.1	22.1 ± 18.9	0.003†
RP	65.7 ± 28.7	25.9 ± 25.6	0.003†
BP	57.2 ± 24.2	35.4 ± 18.0	0.05
GH	51.0 ± 17.1	44.1 ± 23.2	0.5
VT	58.1 ± 20.1	39.3 ± 19.0	0.03†
SF	72.3 ± 28.0	53.6 ± 25.7	0.09
RE	69.6 ± 29.4	42.9 ± 42.6	0.1
MH	69.2 ± 20.9	52.1 ± 22.5	0.05
HAD score‡			
anxiety (definite/doubtful)	5:14	1:3	0.9
depression (definite/doubtful)	31:5	8:2	0.3

* Unless otherwise indicated, values are expressed as the mean ± SD.
† Statistically significant ($p < 0.05$).
‡ Values represent the number of patients whose scores denoted definite anxiety or depression, versus those with doubtful scores.

Spearman rank correlation coefficient for LEF was larger than that for UEF. Also, there was no significant difference in UEF between satisfied and dissatisfied patients. In responses to open-type questions, many patients wrote that the reason why they were dissatisfied was because they could not move by themselves. These details suggest that LEF correlates more directly with satisfaction than UEF.[12] In our experience, many patients decide to undergo surgery because of their fear of being unable to walk. Perhaps because gait disturbance in daily life is a more compelling problem than hand clumsiness, especially in elderly or disabled patients, LEF correlated more strongly with patient satisfaction.

In the present study, the satisfied group had a significantly higher maximum score and maximum recovery rate according to the conventional JOA scoring system. Using a stepwise logistic regression analysis model, we chose maximum recovery rate (conventional JOA) as the independent variable, with satisfaction as the dependent variable. No patients reported being worsened in either the satisfied group or in the neither satisfied nor dissatisfied group. These results suggest that treatment effects as reflected by improvements in conventional JOA score were associated with satisfaction.

There was still controversy over the selection of anterior or posterior surgery for cervical OPLL. In the present study, anterior surgery was basically selected when the occupying ratio of OPLL was greater than 60%, according to previous reports.[9,10,15] As a result, selection of surgical procedures was not a factor influencing patient satisfaction. Appropriate indications for anterior or posterior surgery might lead to successful results in doctor- and patient-based evaluation methods.

Our study had some limitations. First, although the vast majority (96%) of patients who received survey sheets responded, data from 31 patients could not be collected because of the patient's death or an unknown address. If all of these 31 patients were dissatisfied with the results of surgery in the worst-case scenario, the satisfaction rate would decline to 56%. However, in the best-case scenario, the satisfaction rate would rise to 86%. Second, although a stepwise method was used, there was a possibility that multicollinearity existed in the logistic regression analysis. Because some of the JOACMEQ was created with SF-36 as a reference, PF (based on SF-36) might correlate with LEF on the JOACMEQ.

Unlike NRS, there was no significant difference in VAS scores on the JOACMEQ between the satisfied and dissatisfied groups. This discrepancy was thought to have been caused by the fact that the VAS score reported on the JOACMEQ included numbness as well as pain. Numbness was more common, and might be a more acceptable postsurgery symptom than pain for patients with cervical OPLL. Because it was repeatedly explained when obtaining informed consent that numbness was difficult to improve with surgery, patients were thought to be more accepting of numbness. It was reported that unrealistic expectations for surgery decreased satisfaction, and therefore sufficient understanding of the expected results was important for patient satisfaction.[26]

TABLE 4: Summary of clinical data in dissatisfied and neither satisfied nor dissatisfied groups*

Satisfaction	Sex	Age at FU (yrs)	Op Procedures	JOACMEQ Score CF	UEF	LEF	BF	QOL	Reasons (open-type question)
very dissatisfied	M	60	lam	5	53	50	63	15	shoulder stiffness, deterioration of symptoms, difficulty walking
dissatisfied	M	81	lam	0	32	9	13	28	restriction of ROM of neck, difficulty walking
	M	80	lam	20	68	45	94	34	leg numbness
	M	63	lam	100	95	36	38	40	leg numbness & pain
	F	79	lam	50	42	32	38	8	back, neck, & leg pain
	M	68	ACDF	45	95	77	81	45	dislocation of grafted bone & reop, restriction of ROM of neck due to added posterior fusion, leg numbness due to peroneal nerve injury
	F	68	ACDF	40	63	56	56	30	arm & leg pain, difficulty walking
neither satisfied nor dissatisfied	M	81	lam	35	74	55	31	50	difficulty walking
	M	88	lam	5	79	41	50	34	difficulty walking
	F	75	lam	15	42	14	75	44	difficulty walking
	F	65	lam	100	95	59	100	91	difficulty walking
	F	76	lam	25	95	95	94	89	restriction of ROM of neck
	F	83	ACDF	30	37	9	19	32	difficulty walking
	F	61	ACDF	85	95	68	100	31	leg pain

* ROM = range of motion.

Conclusions

The present study demonstrated that 80% of patients were satisfied with the results of surgery for cervical myelopathy due to OPLL. Patient satisfaction was related to QOL, PF (especially LEF), and improvement. Surgery for cervical OPLL was effective when evaluated both by doctor- and patient-based methods.

Appendix: Original Satisfaction Questionnaire

Q1. Are you satisfied with the result of the surgery?
Very satisfied
Satisfied
Neither satisfied nor dissatisfied
Dissatisfied
Very dissatisfied
What are you satisfied or dissatisfied with?

Q2. How has your condition changed since the surgery?
Very improved
Improved
No change
Worsened
Considerably worsened
What are the changes?

Q3. Would you recommend the surgery to a family member or friend suffering from the same disease?
Definitely recommend
Probably recommend
I don't know
Would not recommend
Definitely would not recommend
Why would you recommend or not recommend the surgery?

Q4. Where do you experience body pain?
Neck to shoulders
Arms or hands
Lower body (buttocks, legs, knees)
Please rate the pain:
0: No pain
1: Slight pain
2: Modest pain
3: Moderate pain
4: Severe pain
5: Intolerable pain

TABLE 5: Stepwise logistic regression analysis model with satisfaction as the dependent variable

Parameter (scoring system)*	Chi-Square Value (likelihood ratio test)	p Value
PF (SF-36)	6.4	0.01
QOL (JOACMEQ)	6.4	0.01
LEF (JOACMEQ)	5.1	0.02
max recovery rate (JOA)	1.8	0.18

* Adjusted R^2 = 0.5.

Disclosure

The manuscript does not contain information about medical device(s) or drug(s). Other funds (The Investigation Committee on the Ossification of Spinal Ligaments of the Japanese Ministry of Health, Labor, and Welfare) 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. This study was performed with the aid of the Investigation Committee on the Ossification of the Spinal Ligaments of the Japanese Ministry of Health, Labor, and Welfare. The institutional review board of the authors' institute approved this study.

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Fujimori, Iwasaki. Acquisition of data: Fujimori, Okuda, Oda. Analysis and interpretation of data: Fujimori. Drafting the article: Fujimori. Critically revising the article: Fujimori, Nagamoto, Sakaura. Reviewed final version of the manuscript and approved it for submission: Iwasaki, Yoshikawa. Statistical analysis: Fujimori.

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DIAGNOSTICS

Pathology and Prognosis of Proximal-Type Cervical Spondylotic Amyotrophy

New Assessment Using Compound Muscle Action Potentials of Deltoid and Biceps Brachii Muscles

Yasuaki Imajo, MD, Yoshihiko Kato, MD, Tsukasa Kanchiku, MD, Hidenori Suzuki, MD, Toshihiko Taguchi, MD

Study Design. Case studies of patients with cervical spondylotic amyotrophy (CSA) used compound muscle action potentials (CMAPs) of deltoid and biceps brachii muscles.

Objective: To discuss pathology and prognosis from the magnetic resonance imaging (MRI) and CMAPs of deltoid and biceps brachii muscles.

Summary of Background Data: CSA is a rare type of cervical spondylotic disorder. Selective lesions in ventral nerve roots (VNR) or anterior horns (AH) have been proposed to explain the pathology of CSA, but these are not well understood.

Method: Conservative therapy was performed in 21 patients with the proximal-type CSA. Patients were classified into two groups: 13 with incomplete recovery of deltoid and biceps brachii muscle strength (Group 1) and 8 with complete recovery (Group 2). All underwent MRI. Erb-point–stimulated CMAPs were recorded in the deltoid and biceps. Measurements of CMAPs included negative-peak amplitude from the baseline to peak. The percentage amplitude of CMAPs was calculated in contrast to the opposite side.

Results: Sagittal T2-weighted MRI showed spinal cord compression in all patients from Group 1 and in four patients from Group 2. Deltoid muscle CMAPs: Three patients from Group 1 and all eight patients from Group 2 had a CMAPs' amplitude on the normal side that was greater than 10 mV. Biceps brachii muscle CMAPs: four patients from Group 1 and four patients from Group 2 had a CMAPs' amplitude on the normal side that was greater than 10 mV.

Conclusion: Patients with a CMAPs amplitude on the normal side that exceeded 10 mV had no impingement of the AH. A CMAPs' amplitude that exceeded 10 mV on the normal side and a CMAPs' amplitude of more than 50% on the affected side compared with the normal side indicated slight involvement of VNR. These patients were able to fully recover function.

Key words: cervical spondylotic amyotrophy, compound muscle action potentials, pathology, prognosis. **Spine 2011;36:E476–E481**

Cervical spondylotic amyotrophy (CSA) is a rare type of cervical spondylotic disorder. The clinical characteristics of CSA are severe muscle atrophy and weakness in the upper extremities without significant sensory deficits or myelopathy. CSA can be classified into two types according to the affected muscles in the upper extremities: proximal type (unilateral scapular, deltoid, and biceps brachii muscles) and distal type (triceps, forearm, and hand muscles). Selective lesions in ventral nerve roots or anterior horns in the spinal cord have been proposed to explain the pathophysiology of CSA, but these are not well understood. In this study, we describe 21 patients with proximal-type CSA from the C5–C6 myotome. The pathophysiology is discussed in light of results from magnetic resonance imaging (MRI) and from compound muscle action potentials (CMAPs) of deltoid and biceps brachii muscle.

MATERIALS AND METHODS

Patients

Between 2000 and 2008, conservative therapy was performed in 21 patients with proximal-type CSA. During the follow-up period of at least 1 year (range, 12–72 months; mean, 30 months), most patients received medication, including vitamin B12. Patients were classified into two groups: 13 with incomplete recovery of deltoid and biceps brachii muscle strength (Group 1) and 8 with complete recovery (Group 2). The mean age of Group 1 and Group 2 patients was 63 years (range, 44–78 years) and 54 years (range, 34–64 years), respectively. There were 11 men and 2 women in Group 1, while Group 2 comprised 5 men and 3 women. The clinical symptoms and results of neurologic examination are summarized in Table 1.

All patients had severe unilateral muscle atrophy of the shoulder girdle muscles without gait disturbance. The intrinsic muscles were intact. Muscle strength was evaluated by using manual muscle testing (MMT).[1] In light touch and pinprick

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TABLE 1. Clinical and Neurologic Findings

				MMT*					
	Case	Age	Sex	Deltoid (Initial/ Final)	Biceps Brachii Muscle (Initial/Final)	BTR	TTR	Sensory Disturbance Area†	Medication VB12/ Corticoid
Group 1	1	69	M	P/P	P/P	Absent	N	C6	+/−
	2	72	M	P/P	F/F	Diminished	Absent	...	+/□
	3	64	M	F/F	F/F	Absent	Diminished	...	+/□
	4	67	M	F/F	F/F	Diminished	Diminished	...	+/□
	5	72	M	P/F	F/F	Diminished	Diminished	C5, C6	+/□
	6	56	M	P/F	F/G	Absent	Diminished	...	+/□
	7	63	M	P/P	F/F	Diminished	N	C5	+/□
	8	55	M	F/F	F/F	Diminished	N	...	+/□
	9	67	F	P/F	F/F	Diminished	N	...	+/□
	10	78	M	F/F	P/P	Diminished	Diminished	C5, C6	+/□
	11	73	M	P/P	F/F	Absent	N	...	+/□
	12	44	F	P/P	P/P	Diminished	Diminished	C5, C6	+/□
	13	62	M	P/P	P/P	Diminished	Diminished	C5, C6	+/□
Group 2	14	64	M	F/N	F/N	Diminished	N	...	+/□
	15	56	M	P/N	P/N	Absent	Diminished	C5	+/□
	16	53	F	P/N	G/N	Diminished	Exaggerated	...	+/□
	17	56	M	P/N	G/N	N	Diminished	...	□/□
	18	57	F	P/N	F/N	Diminished	N	...	+/□
	19	53	M	F/N	G/N	Diminished	N	...	□/□
	20	61	M	F/N	F/N	Diminished	N	...	+/□
	21	34	F	P/N	F/N	Diminished	N	...	+/□

Grading Scale of Manual Muscle Testing	
Normal	Contraction against powerful resistance
Good	Contraction against gravity and some resistance
Fair	Contraction against gravity only
Poor	Movement only with gravity eliminated
Trace	Flicker of contraction
Zero	Complete paralysis

**Adapted from Daniels and Worthingham.*
†The impaired level was recorded to the dermatome proposed by Brain and Walton.
+indicates medicated; □, none; BTR, biceps tendon reflex; F, fair; G, good; MMT, manual muscle test; N, normal; P, poor; TTR, triceps tendon reflex; VB12, vitamin B12.

sensation, the impaired levels were recorded according to the dermatome proposed by Brain and Walton.[2] Sensory examination revealed no abnormalities, except for seven patients who had a sensory disturbance for light touch and pinprick in the C5 or C6 dermatome or both.

Patients with cervical disc herniation, ossification of posterior longitudinal ligament of the cervical spine, cervical flexion myelopathy, multifocal motor neuropathy, amyotrophic lateral sclerosis, and subjective symptoms or neurologic findings associated with neuropathy were excluded. No patients were turned out to have amyotrophic lateral sclerosis in this study.

Magnetic Resonance Imaging

All patients underwent MRI with a 1.5-Tesla imaging system. Sections were 5-mm thick, with a 2-mm gap between

TABLE 2. Amplitude of CMAPs and Amplitude Ratio of CMAPs

		Amplitude of CMAPs (mV)					
		Deltoid			Biceps Brachii Muscle		
	Case	Affected Side	Normal Side	Amplitude Ratio (%)	Affected Side	Normal Side	Amplitude Ratio (%)
Group 1	1	1.3	9.9	13	1.8	10.8	17
	2	0.5	8.4	6	4.3	9.0	48
	3	7.0	7.6	92	3.6	7.8	46
	4	0.0	7.7	0	2.0	5.6	36
	5	0.0	7.0	0	2.1	10.8	19
	6	4.0	12.2	33	6.2	9.7	64
	7	0.0	14.5	0	2.2	10.8	20
	8	2.7	10.1	27	3.2	9.8	33
	9	0.5	5.1	10	1.5	8.0	19
	10	0.0	5.8	0	2.8	5.3	53
	11	2.0	6.7	30	3.9	10.5	37
	12	1.4	5.5	25	4.7	5.8	81
	13	3.0	5.7	52	3.3	6.7	49
Group 2	14	7.7	11.8	65	8.0	9.3	86
	15	5.7	10.7	53	8.0	9.6	83
	16	6.6	10.5	63	8.1	9.7	84
	17	6.4	10.8	59	9.1	10.2	89
	18	7.8	11.7	67	9.3	9.9	94
	19	8.4	11.6	72	9.8	13.6	72
	20	8.9	12.8	70	8.0	13.8	58
	21	7.8	11.5	68	6.8	12.2	56

CMAP indicates compound muscle action potentials.

intersections. T1-weighted and T2-weighted sagittal and axial images were obtained.

ELECTROPHYSIOLOGIC INVESTIGATION

All electrophysiologic examinations were performed by using a Nicolet Viking IV instrument (Nicolet Biomedical Madison, Wisconsin). No abnormal findings were observed in the thoracic paraspinal muscles or lower limb muscles (tibialis anterior muscles) with standard needle electromyography. The results of sensory nerve conduction velocity tests for the bilateral median and ulnar nerves were normal in all patients. Erb-point–stimulated CMAPs were recorded in the deltoid and biceps in all patients. A disc electrode, 11 mm in diameter, was placed over the middle of the deltoid as an active electrode, on the acromion as a reference electrode in the deltoid, over the middle of the biceps brachii muscle and on the lateral epicondyle of humerus in the biceps brachii muscle. The skin was prepared with an abrasive solution to reduce impedance, and a ground strap was wrapped around the elbow. The bipolar stimulator consisted of a pair of bare-metal contact surfaces, approximately 3 mm in diameter and with an adjustable interelectrode distance. The stimulus intensity was gradually increased until it no longer altered the size of the recorded response.

Measurements of CMAPs included the negative-peak amplitude from baseline to peak. The percentage amplitude of CMAPs was calculated in comparison to the opposite side.

RESULTS

Magnetic Resonance Imaging

Sagittal T2-weighted MRI showed spinal cord compression in all 13 patients from Group 1. Five had spinal cord compression at C4–C5 and C5–C6; four at C3–C4, C4–C5, and C5–C6; one at C2–C3, C4–C5, and C5–C6; one at C4–C5, C5–C6, and C6–C7; one at C3–C4 and C4–C5; and one at the C5–C6 level. For Group 2, sagittal T2-weighted MRI

showed spinal cord compression in four patients: three at C4–C5 and 1 at C5–C6. Four had foraminal stenosis with a varying degree of disc herniation and with a focal bony spur involving the C4–C5 level in two patients and the C5–C6 level in the other.

ELECTROPHYSIOLOGIC INVESTIGATION

Erb-point–stimulated CMAPs in deltoid and biceps brachii muscles are shown in Table 2.

Deltoid muscle CMAPs

Two of the Group 1 patients had CMAPs that exceeded 50% of the normal side. Three of the patients had a CMAPs' amplitude on the normal side that was greater than 10 mV. For Group 2, all eight patients had CMAPs that exceeded 50% of the normal side. All eight patients had CMAPs' amplitudes on the normal side that were greater than 10 mV.

Biceps brachii muscle CMAPs

Three Group 1 patients had CMAPs that exceeded 50% of the normal side. Four of the patients had a CMAPs' amplitude on the normal side that was greater than 10 mV. For Group 2, eight patients had CMAPs that exceeded 50% of the normal side. Four patients had a CMAPs' amplitude on the normal side that was greater than 10 mV.

Case 8

A 55-year-old man suffered disability from right upper extremity elevation. MMT scores for the deltoid and biceps were P and F, respectively. Sagittal T2-weighted MRI showed spinal cord compression at C4–C5 and C5–C6 levels (Figure 1A). Axial T2-weighted MRI showed impingement of the right C5 nerve root at the C4–C5 intervertebral foramen, the C6 spinal cord segment at the C4–C5 intervertebral level, the right C6 nerve root at the C5–C6 intervertebral foramen, and the C7 spinal cord segment at the C5–C6 intervertebral level (Figure 1B–C).

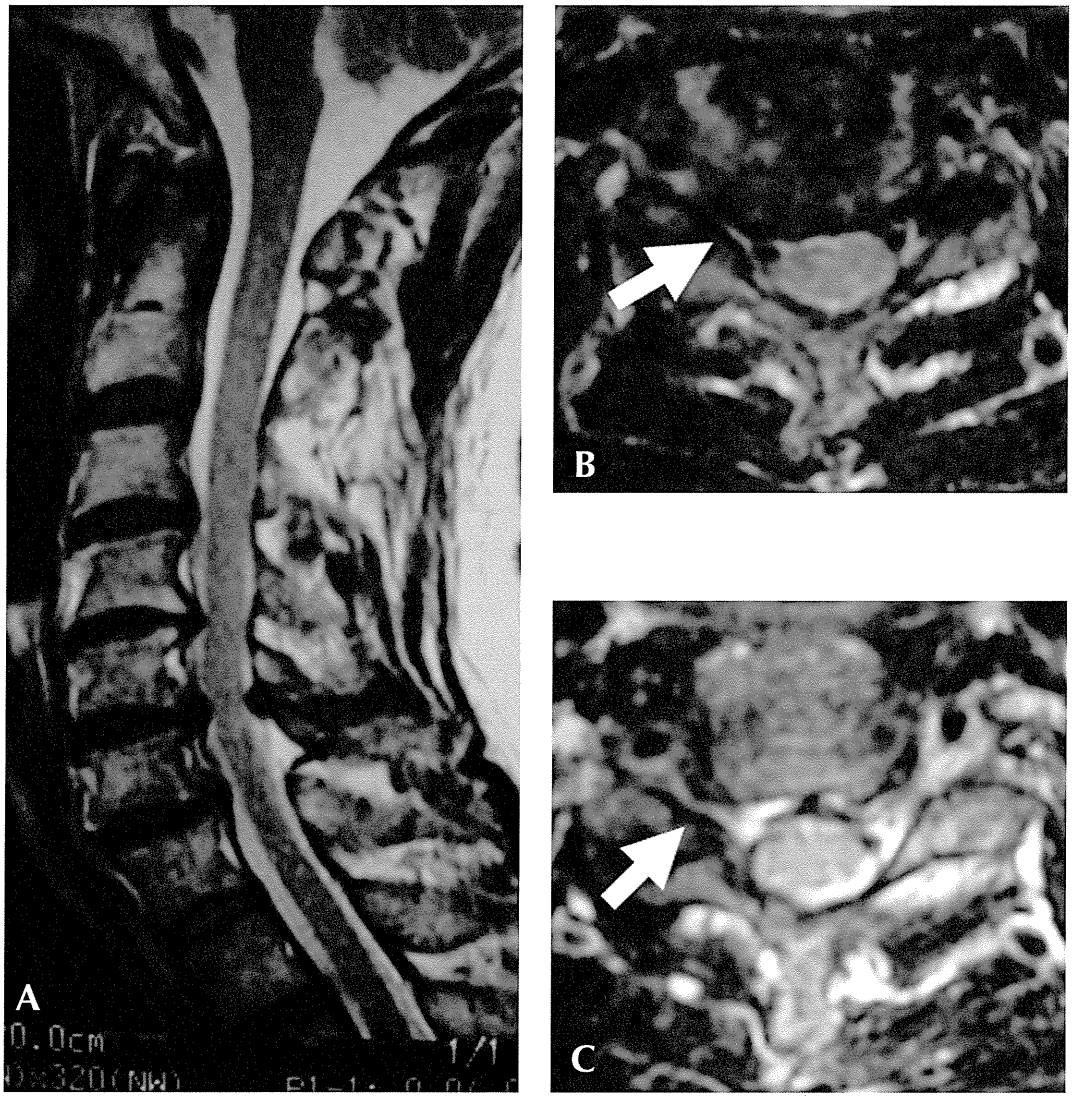

Figure 1. **(A)** Sagittal T2-weighted MRI showed spinal cord compression at the C4–C5 and C5–C6. **(B)** Axial T2-weighted MRI showed impingement of the right C5 nerve root at the C4–C5 intervertebral foramen. **(C)** Axial T2-weighted MRI showed impingement of the right C6 nerve root at the C5–C6 intervertebral foramen.

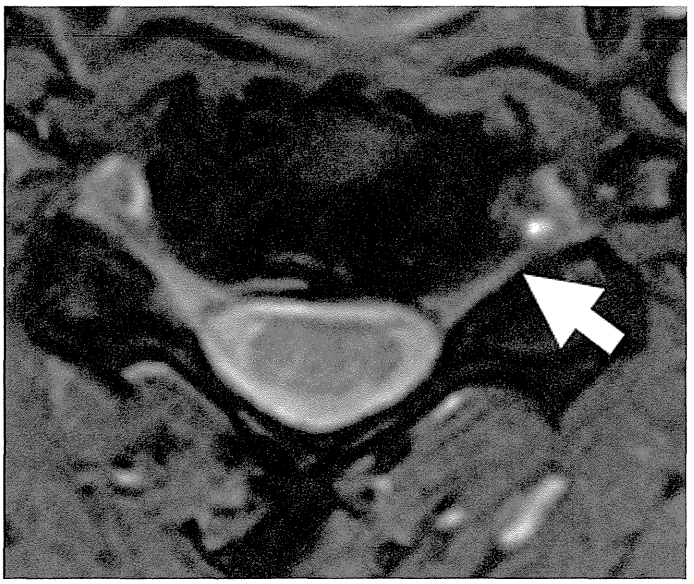

Figure 2. Axial T2-weighted MRI showed impingement of the left C5 nerve root at the C4–C5 intervertebral foramen.

Deltoid CMAPs' amplitudes on the normal and affected sides were 10.1 mV and 2.7 mV, respectively. The percentage amplitude of deltoid CMAPs on the affected side in comparison with the normal side was 27%. Biceps brachii muscle CMAPs' amplitudes on the normal and affected sides were 9.8 mV and 3.2 mV, respectively. The percentage amplitude of biceps brachii muscle CMAPs was 33%. The patient had not recovered deltoid and biceps brachii muscle function after 25 months.

Case 17

A 58-year-old man suffered disability from left upper extremity elevation. MMT scores for the deltoid and biceps brachii muscles were P and F, respectively. No spinal cord compression was visible on sagittal T1-weighted MRI. On axial T2-weighted MRI, the left C5 nerve root at the C4–C5 intervertebral foramen was compressed by a focal bony spur (Figure 2). Deltoid CMAPs' amplitudes on the normal and affected sides were 10.8 mV and 6.4 mV, respectively. The percentage amplitude of deltoid CMAPs on the affected side in comparison with the normal side was 59%. Biceps brachii muscle CMAPs' amplitudes on normal and affected sides were 10.2 mV and 9.1 mV, respectively. The percentage amplitude of biceps brachii muscle CMAPs was 89%. The patient recovered full deltoid and biceps function after 3 months.

DISCUSSION

CSA is the clinical syndrome in cervical spondylosis characterized by severe muscular atrophy in the upper extremity concurrent with absent or insignificant sensory deficit.[3] Whether the pathophysiology of this syndrome involves selective damage to ventral nerve roots or to anterior horns is controversial. Keegan[4] attributed CSA to selective intradural compression of the ventral nerve roots by posterolateral osteophytes. Yanagi *et al*[3] attributed this syndrome to circulatory insufficiency in the regions of the spinal central arteries, as well as selective damage to the anterior horns.[3] Ito *et al*[5] and Kaneko and Kawai[6] reported that both the anterior horns and the ventral nerve roots are compromised by paramedian compression. On the basis of a T2 high signal-intensity area on MRI, Kameyama *et al*[7] reported that impingement of the anterior horn caused CSA. We hypothesized that the pathophysiology of CSA was caused by a combination of lesions in the anterior horns and ventral nerve roots. Accordingly, we have classified 13 types of CSA (Table 3).

TABLE 3. Classified of the Proximal-Type CSA

Type	Impingement of VNR and AH
1	C5VNR
2	C6VNR
3	C5VNR + C6VNR
4	C5AH + C5VNR
5	C5AH + C6VNR
6	C5AH + C5VNR + C6VNR
7	C6AH + C5VNR
8	C6AH + C6VNR
9	C6AH + C5VNR + C6VNR
10	C5AH + C6AH
11	C5AH + C6AH + C5VNR
12	C5AH + C6AH + C6VNR
13	C5AH + C6AH + C5VNR + C6VNR

AH indicates anterior horn; CSA, cervical spondylotic amyotrophy; VNR, ventral nerve root.

Tani *et al*[8] reported that the normal value for deltoid CMAPs in 20 men older than 60 years (range, 62–85 years; mean, 72 years) was 9.7 ± 1.6 mV (mean ± standard deviation). Trojoborg[9] reported that the normal value for biceps brachii muscle CMAPs in four patients older than 65 years (range, 65–74 years) was 9 mV in amplitude. For the present study, we therefore assumed that the normal value for deltoid and biceps brachii muscle CMAPs was 10.0 mV in amplitude. We could not confirm that only smaller amplitudes from the affected side were because of lesions in the anterior horns or ventral nerve roots. However, we believe that a lower amplitude on the bilateral side indicates involvement of anterior horns rather than that of bilateral ventral nerve roots. We hypothesized that patients with a CMAPs' amplitude exceeding 10 mV on the normal side had no impingement of anterior horns. A CMAPs' amplitude that exceeded 10 mV on the normal side and a percentage of more than 50% for CMAPs' amplitude on the affected side in comparison with the normal side indicated slight involvement of ventral nerve roots. A CMAPs' amplitude exceeding 10 mV on the normal side and a CMAPs' ratios of less than 50% on the affected side compared with the normal side indicated severe involvement of ventral nerve roots.

TABLE 4. Pathology of the proximal CSA

Amplitude of CMAPs at Normal Side (mV)	The Percentage of CMAPs at Affected Side (%)	Involvement of Area
>10 mV	>50%	VNR slightly
>10 mV	<50%	VNR slightly
5–10 mV	>50%	AH + VNR slightly
5–10 mV	<50%	AH + VNR slightly

VNR, ventral nerve root; AH indicates anterior horn.

On the contrary, patients in whom the CMAPs' amplitude range was from 5 to 10 mV on the normal side and the percentage amplitude of CMAPs was more than 50% on the affected side compared with the normal side indicated the involvement of the anterior horns and slight involvement of ventral nerve roots. Patients in whom the CMAPs' amplitude range was from 5 to 10 mV on the normal side and the percentage amplitude of CMAPs was less than 50% indicated strong involvement of both anterior horns and ventral nerve roots (Table 4).

It is generally accepted that upper limb muscles are innervated by several nerve roots.[10,11] In general, C5 and C6 nerve roots are distributed to deltoid and biceps brachii muscles.[12,13] According to the results of CMAPs' amplitude and the MRI findings, cases 14, 15, and 16 involved the C5 root and C6 anterior horn. Cases 17 and 19 involved the C5 root. Cases 18, 20, and 21 involved the C6 root. The results for CMAPs' amplitude corresponded with findings from MRI. We confirmed that types one, two, and seven CSA could recover full deltoid and biceps function. In contrast, most Group 1 patients had multiple segmental compression of the spinal cord, making it difficult for them to recover full function. Case 7 had no compression of the spinal cord at C3–C4 and C4–C5, but their C5 root was severely involved. It was difficult for patients with the involvement of C5 anterior horn to recover full function. Fujiwara *et al*[14] and Uchida *et al*[15] reported that surgical treatment of proximal-type CSA was effective. However, we must recognize that type one, two, and seven CSA can recover full deltoid and biceps function. It is important to perform the electrophysiologic examinations.

In conclusion, we confirmed that severe involvement of a single nerve root meant that the patient could not recover full function. We also demonstrated that the pathology and prognosis of proximal-type CSA could be assessed by using CMAPs of deltoid and biceps brachii muscles. Patients with a CMAPs' amplitude on the normal side that exceeded 10 mV had no impingement of the anterior horns. A CMAPs' amplitude that exceeded 10 mV on the normal side and a CMAPs' amplitude of more than 50% on the affected side compared with the normal side indicated slight involvement of ventral nerve roots. These patients were able to fully recover deltoid and biceps function.

➢ Key Points

- ❑ Patients with a CMAPs' amplitude on the normal side that exceeded 10 mV had no impingement of the anterior horn.
- ❑ A CMAPs' amplitude that exceeded 10 mV on the normal side and a CMAPs' amplitude of more than 50% on the affected side compared with the normal side indicated slight involvement of ventral nerve roots. These patients were able to fully recover deltoid and biceps brachii muscles function.

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ORIGINAL ARTICLE

Relative vulnerability of various spinal tracts in C3-4 cervical spondylotic myelopathy: multi-modal spinal cord evoked potentials

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Study design: Retrospective study.
Objective: To investigate the progression of spinal tract lesions in cervical spondylotic myelopathy (CSM) at C3-4 intervertebral level using spinal cord-evoked potensials (SCEPs).
Setting: This study was conducted at the Department of Orthopaedic Surgery, Yamaguchi University Graduate School of Medicine, Japan.
Methods: A total of 30 patients with CSM were investigated in this study. In all patients, only the C3-4 intervertebral level was symptomatic, as shown by examination of SCEPs. SCEPs were recorded following median nerve stimulation (MN-SCEPs), transcranial electric stimulation (TES-SCEPs) and spinal cord stimulation (spinal-SCEPs).
Results: The incidence of abnormalities varied in the order of MN-SCEPs (100%), TES-SCEPs (90%) and spinal-SCEPs (67%). Patients were grouped into three types according to SCEPs: transverse (all SCEPs abnormal), post-erolateral (abnormalities in the MN-SCEPs and TES-SCEPs) and upper limbs sensory (abnormal only for MN-SCEPs). In all, 20 of the 30 patients (67%) were the transverse type, 7 (23%) the post-erolateral type and 3 (10%) the upper limbs sensory type.
Conclusion: The present study showed the lateral part of the posterior funiculus mediating upper limb sensory function was more vulnerable than the lateral corticospinal tract, which is consistent with numbness tending to appear at an early stage of mild CSM.
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Keywords: cervical spondylotic myelopathy; median nerve stimulation; spinal cord evoked potentials; spinal cord stimulation; transcranial electric stimulation

Introduction

Several reports have described the pathology of cervical spondylotic myelopathy (CSM) from autopsy specimens.[1,2] Most of these were obtained from patients with typical spastic paralysis, and involvement of the lateral corticospinal tract was a common finding. Ito[3] reported the progression pattern and histological findings of the lesions in the spinal cord affected by CSM. Atrophy and neuronal loss in the anterior horn and intermediate zone developed first, followed by degeneration of the lateral and posterior funiculus. However, it is not clear which spinal tract is most vulnerable in CSM or how the spinal tract lesions progress from a mild to severe stage. Finger numbness is the most common initial symptom of most patients with mild stage CSM.[4] However, the pathophysiology underlying this finger numbness is presently unclear. Spinal cord-evoked potensials (SCEPs) are useful for evaluating the functional integrity of spinal tracts.[5] We have evaluated electrophysiologically the functions of three spinal tracts and reported in this study our investigation on the correlation between progression of spinal tract lesions in CSM at the C3-4 intervertebral level estimated by multi-modal SCEPs and neurological findings.

Materials and methods

A retrospective study of 122 CSM patients who underwent laminoplasty as well as SCEPs studies between April 1997 and July 2008 was conducted. Written informed consent with the approval of the Human Experimentation Ethics Committee of Yamaguchi University Graduate School of medicine was obtained for preoperative magnetic resonance imaging (MRI) investigation and electrophysiological studies in all patients, and those who fulfilled the following criteria were included in this study.

A diagnosis of myelopathy was established based on the presence of hyperreflexia including positive Hoffmann sign

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and upper extremity sensory disturbance as well as obvious MRI-documented cervical spinal cord compression. Sensory and motor nerve conduction velocities in peripheral nerves were within normal limits. We excluded the patients with myelopathy from other causes such as compression from the ossified posterior longitudinal ligament, disc herniation and trauma and those with radiculomyelopathy.

Of the 122 patients, 30 patients (15 men) selected on the basis of SCEPs abnormalities at the C3-4 intervertebral level were analysed. Their mean age was 71.8 years (range 47–87 years). The mean length of clinical history before admission was 16.5 months (range 2 months–16 years). The mean duration of postoperative follow-up was 1 year and 5 months (range 6 months–7 years and 6 months). The clinical symptoms and results of neurological examination are summarised in Table 1. The area of numbness was determined by asking patients the part of the upper extremity in which they felt numbness according to the dermatome proposed by Brain.[6] Radiographic examinations included plain radiography and preoperative MRI. In all patients treated using laminoplasty, five intervertebral levels (C3-4 to C7-T1) were always decompressed according to the Hattori's method.[7]

Abnormal SCEPs findings at the C3-4 intervertebral level were associated with damage of the long tract. SCEPs following median nerve stimulation (MN-SCEPs), transcranial electric stimulation (TES-SCEPs) and spinal cord stimulation (spinal-SCEPs) were recorded intraoperatively. The MN-SCEPs at the C3-4 intervertebral level are mediated by the lateral parts in the posterior columns (Burdach tract), TES-SCEPs by the lateral corticospinal tract and the N2 components of spinal-SCEPs by the medial parts in the posterior columns (Goll tract). The median nerves were stimulated (square wave pulse, 0.2 ms duration, 3-Hz rate) at the wrist. The stimulus intensity was set at 1.5 times that required to produce a thumb twitch in the awakened condition. TES was delivered as square pulses of 0.2 ms duration and at an intensity of 100 mA through needle electrodes (13R25, Dantec, Denmark) placed on the skull. The anode was placed 7 cm laterally to the right of the Cz position (10–20 International System) on a line joining the external auditory meatus. The cathode was placed on the opposite side. spinal-SCEP was delivered by an epidural catheter electrode inserted into the dorsal epidural space from the C7-T1 and T11-12 interlaminar space. Square wave pulses (0.2 ms duration, 3-Hz rate) were delivered at an intensity of 15–20 mA. Before laminoplasty, all SCEPs were recorded intraoperatively with recording electrodes (13R25) inserted in the ligamentum flavum at each interlaminar space. A reference electrode was inserted into the subcutaneous tissue in the posterior aspect of the neck for recording of MN-SCEPs and spinal-SCEPs. A bipolar recording method was used (active proximal and reference distal) for the recording of TES-SCEPs.

All SCEP signals were amplified and filtered with a bandpass of 20–3000 Hz using a standard evoked potential/

Table 1 Clinical findings

Case	*Gender*	*Ages*	*BTR/TTR*	*MMT (shoulder abduction)*	*Area of numbness*	*PSD (M)*
1	F	80	↑/↑	2	C6	2
2	F	77	↑/↑	2	C6	24
3	F	87	→/↑	3	C5	6
4	F	73	↑/↑	3	C6	24
5	F	80	↑/↑	2	C6	36
6	M	73	↑/↑	3	C6	36
7	M	71	→/↑	4	C6	5
8	M	53	↑/↑	4	C6	13
9	M	64	↑/↑	4	C6	12
10	M	67	↑/↑	4	C6	192
11	F	71	→/↑	5	C6	2
12	F	81	↑/↑	5	C6	9
13	M	76	↑/↑	5	C6	4
14	M	82	↑/↑	4	C6	7
15	M	56	↑/↑	4	C6	6
16	M	59	↑/↑	4	C6	3
17	F	76	↑/↑	4	C6	7
18	F	86	↑/↑	3	C6	4
19	M	87	→/↑	5	C6	18
20	M	58	↑/↑	4	C6	2
21	F	80	→/↑	5	C6	10
22	F	69	→/↑	5	C6	5
23	F	78	↑/↑	5	C6	12
24	M	66	↑/↑	4	C6	3
25	F	47	↑/↑	5	C6	7
26	M	78	↑/↑	5	C6	22
27	M	73	↑/↑	5	C6	6
28	F	77	–/→	5	C6	3
29	F	80	→/→	5	C6	3
30	M	48	→/→	5	C6	12

Abbreviations: Area of numbness, according to the dermatome proposed by Brain; BTR, biceps tendon reflex; M, month; MMT, manual muscle testing; PSD, preoperative symptom duration; TTR, triceps tendon reflex; ↑, hyper-reflex; →, normal; –, absence.

electromyography instrument (Nicolet Viking, Nicolet Biomedical USA, Middleton, WI, USA). Averages from 100 to 200 MN-SCEP, 40–60 TES-SCEP and 20–30 spinal-SCEP responses were obtained. Two different averaged responses were superimposed and displayed.

In MN-SCEPs, abnormality was determined from the amplitude ratio of spinal responses at each intervertebral level to that recorded at the C6-7 intervertebral level as reported earlier.[8] The lower limits of the amplitude ratio were 0.4 for C3-4 intervertebral level. In TES-SCEPs and spinal-SCEPs, intervertebral levels with a marked reduction in size of the negative peak (reduction of $>50\%$) were considered as significant.[9,10]

SCEPs findings were compared with clinical symptoms and signs. It was reported that weakness of shoulder abduction, hyperreflexia of biceps tendon reflex (BTR) and the area of numbness were useful factors related to longitudinal level diagnosis in CSM at the C3-4 intervertebral level.[11,12]

Statistical analysis was performed using the Mann–Whitney U test. $P<0.05$ was considered statistically significant.

Results

As shown in Table 2, the incidence of abnormalities varied in the order of MN-SCEPs (100%), TES-SCEPs (90%) and spinal-SCEPs (67%). The patients were grouped into three types according to SCEPs results. All SCEPs were abnormal in the transverse type (TT) (Figure 1), abnormalities in MN-SCEPs and TES-SCEPs were observed in the post-erolateral type (PT) (Figure 2), while only MN-SCEPs were abnormal in the upper limbs sensory type (UT) (Figure 3). In all, 20 of 30 patients (67%) were classified as the TT, 7 (23%) as the PT and 3 (10%) as the UT (Table 3). Hyperreflexia of BTR was correlated with involvement of the lateral corticospinal tract. A total of 21 of 30 patients (70%) showed hyperreflexia of BTR and this was observed in 78% (21/27) of the TT and PT but in none of the three UT. Between two types with and without involvement of the lateral corticospinal tract, the incidence of hyperreflexia of BTR showed significant difference ($P<0.03$).

In all, 17 of 30 patients (57%) showed weakness of shoulder abduction and this feature was again restricted to patients with the TT and PT. Hyperreflexia of BTR and weakness of shoulder abduction were closely correlated with involvement of the lateral corticospinal tract. All patients felt numbness in all fingers, but only one patient had numbness around the shoulder of the C5 segmental region. Preoperative sagittal T2-weighted MRI showed intra-

Table 2 Spinal cord-evoked potentials (SCEPs) and incidence of abnormality

Types of SCEPs	*Incidence*
MN-SCEPs	100%
TES-SCEPs	90%
Spinal-SCEPs	67%

Abbreviations: MN-SCEPs, spinal cord-evoked potentials following median nerve stimulation; Spinal-SCEPs, spinal cord-evoked potentials following spinal cord stimulation; TES-SCEPs, spinal cord-evoked potentials following transcranial electric stimulation.

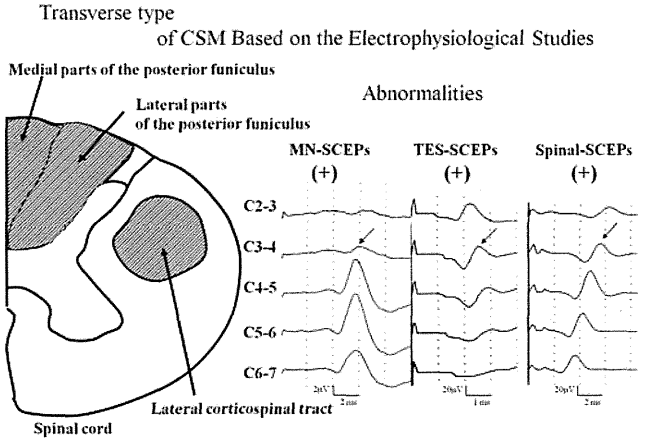

Figure 1 Transverse type showed involvement of medial and lateral parts in the posterior funiculus and lateral corticospinal tracts. Abnormalities were observed in all SCEPs (arrows).

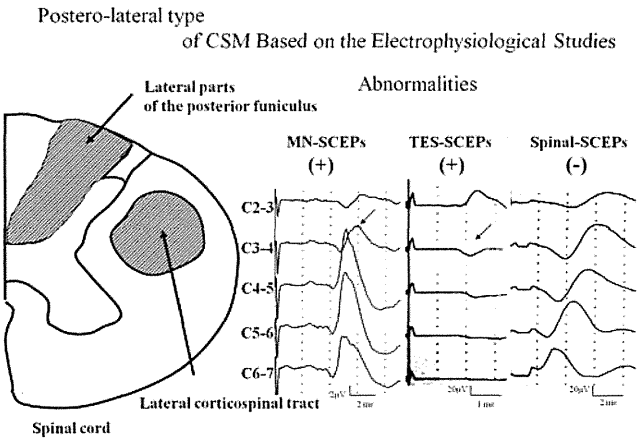

Figure 2 Postero-lateral type showed involvement of lateral parts of the posterior funiculus and lateral corticospinal tracts. Abnormalities were observed in the MN-SCEPs and TES-SCEPs (arrows).

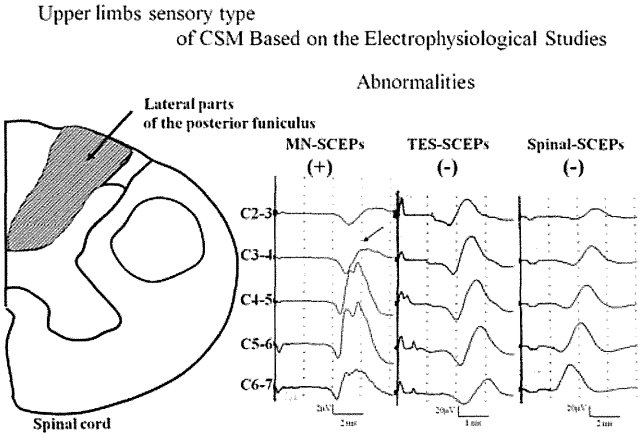

Figure 3 UT showed involvement of lateral parts in the posterior funiculus. Only the MN-SCEPs were abnormal (arrow).

Table 3 Types of CSM based on the electrophysiological studies

Case	*MN-SCEPs*	*TES-SCEPs*	*Spinal-SCEPs*	*Electrophysiological classification*
1	C3/4	C3/4	C3/4	Transeverse
2	C3/4	C3/4	C3/4	Transeverse
3	C3/4	C3/4	C3/4	Transeverse
4	C3/4	C3/4	C3/4	Transeverse
5	C3/4	C3/4	C3/4	Transeverse
6	C3/4	C3/4	C3/4	Transeverse
7	C3/4	C3/4	C3/4	Transeverse
8	C3/4	C3/4	C3/4	Transeverse
9	C3/4	C3/4	C3/4	Transeverse
10	C3/4	C3/4	C3/4	Transeverse
11	C3/4	C3/4	C3/4	Transeverse
12	C3/4	C3/4	C3/4	Transeverse
13	C3/4	C3/4	C3/4	Transeverse
14	C3/4	C3/4	C3/4	Transeverse
15	C3/4	C3/4	C3/4	Transeverse
16	C3/4	C3/4	C3/4	Transeverse
17	C3/4	C3/4	C3/4	Transeverse
18	C3/4	C3/4	C3/4	Transeverse
19	C3/4	C3/4	C3/4	Transeverse
20	C3/4	C3/4	C3/4	Transeverse
21	C3/4	C3/4	WNL	Postero-lateral
22	C3/4	C3/4	WNL	Postero-lateral
23	C3/4	C3/4	WNL	Postero-lateral
24	C3/4	C3/4	WNL	Postero-lateral
25	C3/4	C3/4	WNL	Postero-lateral
26	C3/4	C3/4	WNL	Postero-lateral
27	C3/4	C3/4	WNL	Postero-lateral
28	C3/4	WNL	WNL	Upper limbs sensory
29	C3/4	WNL	WNL	Upper limbs sensory
30	C3/4	WNL	WNL	Upper limbs sensory

Abbreviations: CSM, cervical spondylotic myelopathy; MN-SCEPs, spinal cord-evoked potentials following median nerve stimulation; Spinal-SCEPs, spinal cord-evoked potentials following spinal cord stimulation; TES-SCEPs, spinal cord-evoked potentials following transcranial electric stimulation; WNL, within normal limit.

medullary, high signal intensity changes at the C3-4 level in 17 of 30 (57%) patients. High-signal intensity areas were observed in 55% (11/20) of the TT, 57% (4/7) of the PT and 66% (2/3) of the UT. Preoperative axial T2-weighted MRI revealed that small symmetric intramedullary high-signal intensity areas, a so-called snake eyes appearance were observed in 35% (7/20) of the TT. The presence or absence of high-intensity areas on MRI did not correlate with the severity of myelopathy before surgery ($P>0.05$). For clinical assessment, the Japanese Orthopaedic Association (JOA) scoring system for cervical myelopathy was employed (Table 4).[13,14] The JOA scores were 7.7 points before surgery (UT: 13points, PT: 9.8 points, TT: 6.2 points) and 11.2 points at the final follow-up (UT: 14.8 points, PT: 13.2 points, TT: 10.1 points).

Between UT and PT, preoperative JOA score revealed significant difference ($P<0.04$). Between UT and TT, preoperative and postoperative JOA score revealed significant difference ($P<0.006$ and $P<0.007$, respectively). Between PT and TT, preoperative and postoperative JOA score revealed significant difference ($P<0.004$ and $P<0.008$, respectively). Between UT and PT, postperative JOA score revealed no significant difference ($P>0.05$).

Discussion

Kokubun and Hirabayashi[11,12] described neurogenic findings related to longitudinal level diagnosis of CSM at the C3-4 level (Table 5). Clinical symptoms were different according to the degree of spinal cord compression. The progression of spinal tract lesions was investigated in this study using SCEPs. We could not, however, describe the involvement of anterior funiculus and spinothalamicus tracts in this study. Kameyama[15] reported that anterior spinal tracts with severe CSM showed almost no pathological features.

The UT was observed in mild CSM at early stages. The mean preoperative symptom duration was 16.5 months (the UT: 6 months, the PT: 9.4 months, the TT: 19.4 months). Duration of symptoms and preoperative neurological function may commonly affect surgical outcome. These results demonstrate that the most frequent initial symptom in CSM is finger numbness.[4] All three patients with the UT had finger numbness and clumsiness of hands. Concomitant abnormality of MN-SCEPs correlated well with these symptoms. However, it is still uncertain whether the cause of numbness is involvement of the posterior horn or posterior funiculus.[16] If the cause of numbness is involvement of the posterior horn, most patients with CSM at the C3-4 level would be expected to show numbness at the C5 dermatome. However, this was observed in only one of 30 patients (3%). All 30 patients showed numbness in all five fingers. Involvement of the posterior horn cannot explain the cause of numbness. Finger numbness could be associated with involvement of the lateral parts of the posterior funiculus. Chang[17] reported that high cervical cord compression might produce dysfunction of the dorsal column caudal to the direct compressive sites, and the funiculus cuneatus of C6-8 cord was most affected in high cervical myelopathy. Median nerve is formed by the union of the lower cervical nerve roots (C6-C8). MN-SCEPs at the C4-5, C5-6 and C6-7 intervertebral levels include synapse-dependent component. However, MN-SCEPs at the C3-4 intervertebral level are synapse-independent probably originating from the lateral parts of the posterior funiculus (C6-8), which could explain that all patients felt numbness in all fingers (C6, C7 and C8 segmental regions)

Ogino[18] reported clinicopathological correlations with neurological findings in CSM at the terminal stage. They described that the lateral corticospinal tracts were more vulnerable than the posterior funiculus. Ito[3] reported a common pattern of lesion progression in CSM that involved initial atrophy and neuronal loss in the anterior horn and intermediate zone, followed by degeneration of the lateral and posterior funiculus. Marked atrophy eventually developed throughout the entire grey matter and severe degeneration occurred in the lateral funiculus. Patients in these reports showed moderate to severe CSM, however, those grouped into the UT were mild CSM. The current results are therefore different to these previous pathological findings.

Mizuno[19] reported that patients with single-level snake eyes appearance had significant upper-limb motor weakness. Damage of the anterior horn will cause muscle weakness in restricted region of upper extremities. In all, 35% (7/20) of

Table 4 Japanese orthopaedic association scoring system for cervical myelopathy

A. Motor function	
I. Fingers	
0	Unable to feed oneself with any tableware including chopsticks, spoon, or fork and/or unable to fasten buttons of any size
1	Can manage to feed oneself with a spoon and/or a fork but not with chopsticks
2	Either chopstick-feeding or writing is possible but not practical, and/or large buttons can be fastened
3	Either chopstick-feeding or writing is clumsy but practical, and/or cuff buttons can be fastened
4	Normal
II. Shoulder and elbow (evaluated by MMT score of the deltoid or biceps muscles, whichever is weaker)	
−2	MMT 2 or less
−1	MMT 3
−0.5	MMT 4
0	MMT5
III. Lower extremity	
0	Unable to stand up and walk by any means
0.5	Able to stand up but unable to walk
1	Unable to walk without a cane or other support on a level
1.5	Able to walk without support but with a clumsy gait
2	Walks independently on a level but needs support on stairs
2.5	Able to walk independently when going upstairs, but needs support when going downstairs
3	Capable of fast but clumsy walking
4	Normal
B. Sensory function	
I. Upper extremity	
0	Complete loss of touch and pain sensation
0.5	50% or less normal sensation and/or severe pain or numbness
1	More than 60% normal sensation and/or moderate pain or numbness
1.5	Subjective numbness of slight degree without any objective sensory deficit
2	Normal
II. Trunk	
0	Complete loss of touch and pain sensation
0.5	50% or less normal sensation and/or severe pain or numbness
1	More than 60% normal sensation and/or moderate pain or numbness
1.5	Subjective numbness of slight degree without any objective sensory deficit
2	Normal
II. Lower extremity	
0	Complete loss of touch and pain sensation
0.5	50% or less normal sensation and/or severe pain or numbness
1	More than 60% normal sensation and/or moderate pain or numbness
1.5	Subjective numbness of slight degree without any objective sensory deficit
2	Normal
C. Bladder function	
1	Urinary retention and/or incontinence
2	Sense of retention and/or dribbling and/or thin stream and/or incomplete continence
3	Urinary retardation and/or pollakiuria
4	Normal

Abbreviation: MMT, manual muscle test.
Total for normal patient: 17.

Table 5 Neurological findings in CSM at the C3-4 intervertebral lesion

Neurological findings	*Kokubun (n = 24)*	*Hirabayashi (n = 7)*	*Our findings (n = 30)*
Dysthesia(C6-8)	90%	67%	97%
Hyperreflexia of BTR	100%	67%	70%
Weakness of shoulder abduction	83%	50%	57%

Abbreviation: BTR: biceps tendon reflex; CSM, cervical spondylotic myelopathy.

the TT with snake eyes appearance revealed muscle weakness on shoulder abduction.

Hyperreflexia of BTR was frequently seen and was observed in 78% of patients with involvement of lateral corticospinal tracts. Mild involvement of lateral corticospinal tracts was associated with normal BTR. Weakness of shoulder abduction was observed in 63% of patients with involvement of lateral corticospinal tracts. We considered that involvement of long tracts in CSM occurred initially in the lateral parts of the posterior funiculus (abnormalities in MN-SCEPs only), followed by the lateral corticospinal tract (abnormalities in the TES-SCEPs) and eventually the medial parts of the posterior funiculus (abnormalities in spinal-SCEPs).

For further work, we will analyse patients selected on the basis of SCEPs abnormalities at the C4-5 intervertebral level. MN-SCEPs recorded at the C4-5 intervertebral level are post-synaptic potentials. Posterior horns are estimated by MN-SCEPs recorded at the C4-5 intervertebral level. In addition, SCEPs following ulnar nerve stimulation (UN-SCEPs) are recorded intraoperatively. The UN-SCEPs at the C4-5 intervertebral level are mediated by the lateral parts of the

posterior columns. We will evaluate electrophysiologically the functions of three spinal tracts and posterior horns at the C4-5 intervertebral level.

Conclusions

We have presented 30 patients with CSM at the C3-4 intervertebral level determined by SCEPs findings. Although involvement of the anterior spinal tract was unknown, this study showed the lateral parts of the posterior funiculus mediating upper limb sensory function was more vulnerable than the lateral corticospinal tract. We confirmed that the lateral parts of the posterior funiculus were most vulnerable in three spinal tracts in this study.

Finger numbness in mild, early stage CSM was associated with this pathology.

Conflict of interest

The authors declare no conflict of interest.

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The authors sincerely dedicate this study to the late Dr Kazuo Kaneko who originally devised this pathology.

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ORIGINAL PAPER

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Transplantation of neurospheres derived from bone marrow stromal cells promotes neurological recovery in rats with spinal cord injury

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Abstract Previous studies have revealed that cell therapy using bone marrow stromal cells (BMSCs) could promote motor functional recovery in animals with spinal cord injury (SCI). We describe here the development of cell biology technique and the experimental study of regeneration in SCI. The aim of this study was to investigate the potential for neurological recovery by transplantation neurospheres (NS) derived from BMSCs into thoracic SCI. Adult Fisher rats were used: 45 were subjected to complete thoracic SCI performed by the balloon compression method. BMSCs were cultured in vitro to obtain NS. Seven days after thoracic SCI, groups of 15 rats each received transplants of BMSCs-NS (group A), BMSCs (group B), or injection of medium only (group C) into the SCI lesion. Rats from each group were evaluated and compared longitudinally for motor function recovery. The spinal cords (SC) of injured rats were harvested at day 21 or day 42 and prepared for histological analysis. Five weeks after transplantation, many neuronal or axonal sproutings were observed and replaced by host cells in the SCI lesion of group A. Also, transplanted BMSCs-NS expressed neuronal lineage markers. Transplanted rats could walk with weight bearing and showed recovered motor evoked potentials (MEPs).

Key words Spinal cord injury · Cell therapy · Bone marrow stromal cell · Neurosphere · Motor evoked potential · Cell sprouting

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Introduction

Severe spinal cord injury (SCI) usually results in long-lasting deficits involving partial or complete paralysis and loss of sensation below the level of the injury. Cell transplantation to repair SCI is an active area of research with the goal of recovering the functional deficit.[1] The central nervous system (CNS) has long been regarded as incapable of regeneration, and hence the recent discovery of stem cell populations in the CNS has generated intense interest.[1,2] Neural stem cells (NSCs) are capable of undergoing expansion and differentiating into neurons, astrocytes, and oligodendrocytes in vitro and in vivo. However, NSC sources are deep inside the brain, and this inaccessibility severely limits their clinical utility. Identification of alternate sources of neural cells is therefore highly desirable. Multipotent stem cells, which have been detected in multiple tissues in adult mammals, participate in normal replacement and repair[3–5] while undergoing self-renewal. BMSCs contain a small fraction of stem cells that can differentiate into neurons or glial cells.[1,3–12] Transplantation of such stem cells has the potential to promote functional recovery after SCI.[10,12–15] BMSCs have potential clinical use as autografts whereas embryonic stem (ES) cells or stem cells from fetuses can be used as allografts.[15] Previous reports have shown that transplantation of only BMSCs after SCI was insufficient for high-order functional recovery because few BMSCs differentiate into neuronal cells.[9,12,13] We have previously reported an original cell line that collects neural stem cell-like masses from BMSCs.[16] This new cell biology technique has the potential to resolve problems with recent treatment for SCI using NSCs or BMSCs. The transplantation of BMSC-neurospheres (BMSCs-NS) in rats with SCI was investigated here, and a good level of neurological recovery was demonstrated. The present cell biology technique provides a new approach for SCI therapy involving autograft cell transplantation of neural stem cells.[16]

Materials and methods

BMSCs culture

BMSCs obtained from thigh bones of green fluorescent protein (GFP) rats[17] (mean age, 8 weeks; hemizygous GFP transgenic Wistar rats provided by Health Science Research Resources Bank, Japan) were cultured in Dulbecco's modified Eagle's medium (DMEM); Gibco BRL, Rockville, MD, USA) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin, and 100 mg/ml streptomycin.[16] The green fluorescent protein (GFP) is a protein composed of 238 amino acid residues (26.9kDa) that exhibits bright green fluorescence when exposed to blue light. In cell and molecular biology, the GFP gene is frequently used as a reporter of expression. Almost all tissues of the GFP transgenic rat, including BMSCs, are green under excitation light. The cells were incubated in dishes at 37°C in 5% CO_2 for 5 days, and nonadherent cells were removed by replacing the medium. After reaching confluence at approximately 2–3 weeks, the cells were harvested with 0.05% w/v trypsin and 0.02% w/v ethylenediaminetetraacetic acid (EDTA) in phosphate-buffered saline (PBS; pH 7.4) for 5 min at 37°C, replated, cultured again for 1 week, and finally harvested. Cells used in this study were harvested after three to five passages.

BMSCs-NS induction

Subconfluent cultures of BMSCs were changed to differentiation media that was a modification of that used by Suzuki et al.[16] Twenty-four hours before neuronal induction, the DMEM supplemented with 10% FBS, 100 U/ml penicillin, and 100 mg/ml streptomycin was replaced with preinduction media consisting of DMEM/10% FBS/1 mM β-mercaptoethanol. To initiate neuronal differentiation, the preinduction media was removed and cells transferred to neuronal induction media composed of DMEM/1% FBS and containing 1% dimethyl sulfoxide (DMSO) and 200 μM butylated hydroxyanisole. After 12–72 h, many adherent cells detached from the dishes. Some of these floating cells changed into neural-like cells and were positive for nestin, a marker of neural progenitors. After counting and testing their viability, cells were cultured in medium containing Neurobasal A (Gibco-BRL), 100 U/ml penicillin G, 100 U/ml streptomycin, 2 mM L-glutamine, supplemented with B-27 (Gibco-BRL) and basic fibroblast growth factor (bFGF; 40 ng/ml; Kaken Pharmaceutical). This medium was a modification of that used by Svendsen et al.[18] Cells were maintained in this medium, and the bFGF was replaced each day. Spheroids (clusters of floating cells) became apparent after 7–15 days.

Spinal cord injury (SCI) model and transplantation

The balloon compression model using a 2 Fr. Fogarty catheter (M&I Medical Sales, Miami, FL, USA) was used for complete SCI in rats.[19,20] Studies were performed in 48 adult female Fisher rats weighing approximately 170 g (8 weeks of age) at the beginning of the experiment. Under anesthesia with intramuscular ketamine (64 mg/kg) and xylazine (4.5 mg/kg), partial laminectomy of the T9 vertebra was performed on 45 rats. A 2 Fr. Fogarty catheter was placed into the epidural space and the balloon tip inserted at the T10 level. The balloon was inflated with 70 μl saline for 3 seconds under the T9–T10 lamina. All rats showed complete paraplegia (BBB score of 0) after balloon compression.[20,21] Partial laminectomy was performed in 3 rats as a sham operation group. Transplantation was performed 7 days after SCI using a Hamilton syringe. Each rat was transplanted with 50 μl gel or medium containing cells into the injured spinal cord.[10] A total of 10 rats received 2×10^7 BMSCs-NS within 0.1% collagen gel for preparation before transplantation (group A). Another 10 rats received noninduced 2×10^7 BMSCs in 0.1% collagen gel (group B). Finally, 10 rats were injected with medium only (group C). Animal experiments were carried out in accordance with the Guidelines for Animal Experiments at Yamaguchi University.

Behavioral and electrophysiological evaluations

Animals were carefully maintained in an air-conditioned room at 22°C with appropriate humidity and had free access to food and water. Behavioral evaluation was performed using the open-field BBB scoring system.[21] Scores from 0 (complete paralysis) to 21 (normal gait) were recorded every day for 6 weeks after SCI. Scoring was performed by an investigator blinded to the treatment status. Significant differences between BBB scores were examined using the repeated measures analysis of variance (ANOVA) and Bonferroni post hoc analysis for multiple group comparisons to determine the statistical significance of the results. All values are given as mean ± SEM. Values of $P < 0.01$ were considered as statistically significant.

Motor evoked potentials (MEPs) following transcranial electric train stimulation were recorded from bilateral gastrocnemius muscles in rats anesthetized with ketamine.[22,23] Groups A–C and naïve rats were examined longitudinally every week before and after SCI. For electrical stimulation, bipolar needle electrodes were fixed onto the skull surface. The anodal (+) electrode was inserted percutaneously into the scalp and the cathodal (–) electrode was placed in the mouth.[23] The train was two times; the intensity of the stimulus was about 15 mA of 0.2-ms duration. The interstimulus interval (ISI) was at 2 ms. After the last MEP recording, all rats were checked for disappearance of the MEP wave following transection of the sciatic nerve.

Histological evaluations

Injured rat SCs were harvested at day 21 and day 42 after SCI. Animals were deeply anesthetized by intraperitoneal injection of pentobarbital sodium (100 mg/kg) and transcardially perfused with saline for 5 min followed by 4% para-