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DIAGNOSTICS

Modified K-Line in Magnetic Resonance Imaging Predicts Insufficient Decompression of Cervical Laminoplasty

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Study Design. A retrospective single-center study.

Objective. To clarify preoperative factors predicting unsatisfactory indirect decompression after laminoplasty in patients with cervical spondylotic myelopathy.

Summary of Background Data. Many authors have shown that inadequate indirect decompression after laminoplasty can inhibit neural recovery and should be considered a complication. We previously demonstrated that residual anterior compression of the spinal cord (ACS) impaired recovery of upper extremity motor function. Although the K-line has been established as a predictive index indicating that laminoplasty is required in patients with ossification of the posterior longitudinal ligament, it remains unclear what preoperative factors can predict insufficient posterior cord decompression in patients with cervical spondylotic myelopathy.

Methods. Forty-six consecutive patients who underwent laminoplasty for the treatment of cervical spondylotic myelopathy at our hospital were reviewed. A modified K-line was defined as the line connecting the midpoints of the spinal cord at C2 and C7 on a T1-weighted sagittal magnetic resonance image. We also determined the minimum interval between the tip of local kyphosis and a line connecting the midpoint of the cord at the level of the inferior endplates of C2 and C7 (INT_{min}) on the midsagittal image. Data analysis involved logistic regression and receiver operating characteristic curve analysis to select the most valuable index for predicting postoperative ACS.

Results. Ten patients had ACS immediately after laminoplasty. Logistic regression analysis showed that INT_{min} was a significant predictive factor for the occurrence of postoperative ACS (odds ratio = 0.485; 95% confidence interval = 0.29–0.81; $P = 0.02$). Receiver operating characteristic curve analysis showed an area under the curve of 0.871. A cutoff of 4.0 mm had a sensitivity of 80% and a specificity of 80.6% for prediction of postoperative ACS.

Conclusion. The parameter INT_{min} correlated with the occurrence of postoperative ACS. A cutoff point of 4.0 mm is most appropriate for alerting spine surgeons to a high likelihood of postoperative ACS.

Key words: cervical spondylotic myelopathy, laminoplasty, anterior compression of spinal cord, postoperative anterior compression. **Spine 2013;38:496–501**

Laminoplasty (LAMP) has been adopted by many surgeons[1–5] as an effective and relatively safe method of treating cervical spondylotic myelopathy (CSM). The procedure can provide sufficient decompression for multisegmental stenotic lesions. However, preoperative kyphotic alignment or a large anterior disc herniation often results in residual anterior compression of the spinal cord (ACS) that affects postoperative neural recovery,[6–8] probably because impinging posterior vertebral bodies or longitudinal ligament shifts the spinal cord anteriorly. Notably, several authors[9,10] have reported limitations of the indirect decompression procedure *via* LAMP for treating ossification of the posterior longitudinal ligament (OPLL), resulting in postoperative ACS.[11–13] Fujiyoshi *et al*[14] developed the K-line, which connects the midpoints of the spinal canal at C2 and C7 on neutral lateral radiographs, as a means of predicting poor clinical outcome in patients with OPLL. They classified patients with OPLL into 2 groups: K-line (+) and K-line (−). They concluded that sufficient posterior shift of the spinal cord and neurological improvement were not obtained after posterior decompression surgery in patients in the K-line (−) group, in whom anterior compression of the OPLL exceeds the line. However, despite the importance of predicting the occurrence of ACS after LAMP for the treatment of CSM, there are as yet no reports of reliable predictive factors used by spine surgeons.

This study investigated, using a modification of the above-mentioned K-line for magnetic resonance imaging (MRI), whether the occurrence of ACS is significantly correlated with preoperative anterior clearance of the spinal cord and sought to identify preoperative factors for predicting insufficient indirect decompression *via* LAMP in the treatment of CSM.

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MATERIALS AND METHODS

Patients and Methods

We conducted a retrospective, observational, single-center study of posterior decompression with LAMP for the treatment of CSM. The study was carried out with the approval of the institutional ethics committee (#1061). Patients with cervical myelopathy caused by spondylosis were included in the study. Exclusion criteria were myelopathy caused by single-level disc herniation or OPLL, a history of cervical spine surgery, postoperative epidural hematoma, and cases in which preoperative and postoperative magnetic resonance (MR) image could not be obtained. Patients who had cervical kyphosis in which the sagittal lordotic angle was greater than 10° were not enrolled in this study.

Forty-six consecutive patients who underwent LAMP for the treatment of CSM at our hospital between 2000 and 2010 were evaluated. All patients were followed for more than 2 years.

Operative Technique

Expansive LAMP was performed as described by Miyazaki and Kirita.[15] Briefly, this procedure at C3–C7 included removing the C4–C6 processes, splitting the laminae at the center, making bilateral gutters at C3–C6, and fenestration at the cephalad portion of the C7 lamina using a high-speed air-burr drill. LAMP at C3–C6 comprised splitting the C3–C6 laminae without fenestration at the C7 lamina. The laminae were kept open with anchor sutures in the deep fascia, and small bone chips made from the spinous processes were inserted into the gap between the laminae and the facets on the hinge side. Patients were instructed to wear a neck collar for 2 to 4 weeks postoperatively.

Evaluations

Clinical Findings

The Japanese Orthopaedic Association (JOA) scoring system[16] was used to evaluate the severity of cervical myelopathy before and after surgery. The recovery rate (RR) was calculated using the method of Hirabayashi *et al*[17] to compare pre- and postoperative JOA scores.

Radiological Evaluations

Radiographical studies were conducted in all patients and results were evaluated by 2 independent spine surgeons. MR image was obtained both before and within 3 months after surgery in all patients. All MR images were obtained on a 1.5 T scanner (Signa HDxt 1.5T; GE Healthcare, Waukesha, WI), and the MRI protocol consisted of following conventional MRI sequence parameters: (1) sagittal T1-weighted spin-echo: repetition time (TR)/ echo time (TE), 480/9 ms, spacing 3 mm; (2) sagittal T2-weighted spin-echo: TR/TE, 3000/85 ms, spacing 3 mm; (3) transaxial T1-weighted spin-echo: TR/TE, 460/10 ms; and (4) transaxial T2-weighted SE: TR/TE, 4020/110 ms. We measured the interval between the midpoint of the cord and the posterior edge of the anterior element such as a bulging disc or intervertebral spur formation before and after surgery and then calculated how much the cord had migrated posteriorly at each segment (Figure 1A). Referring to the K-line,[14] we modified it to connect instead the midpoints of the spinal cord at the level of the inferior endplates of C2 and C7 on T1-weighted MR image (mK-line; Figure 1B). On the basis of the mK-line, we defined INT_{min} as the minimum interval between the mK-line and the anterior compression factor on the midsagittal image. Furthermore, whether indirect decompression could be done or not was evaluated immediately after surgery. The postoperative ACS was investigated using the criteria for defining significant ACS as follows: (1) effacement of the anterior cerebrospinal fluid buffer on T2 sagittal and axial images and (2) evidence of anterior compression of cord substance on the T1 sagittal and axial images.[18] On radiographs, cervical sagittal alignment (C2–C7 lordotic angle), determined as tangential lines on the posterior edges of the C2 and C7 bodies, and the preoperative local segmental (LS) angle, defined as the angle between the line drawn at the posterior margin of the cranial and caudal vertebral bodies at the segment responsible in which INT_{min} should be evaluated, were measured in a neutral position.

Statistical Analysis

To identify the most crucial risk factors for poor surgical outcomes, risk factor analysis was performed by multivariate logistic regression with a forward stepwise procedure ($P < 0.1$ for entry), using SPSS for Windows version 20.0

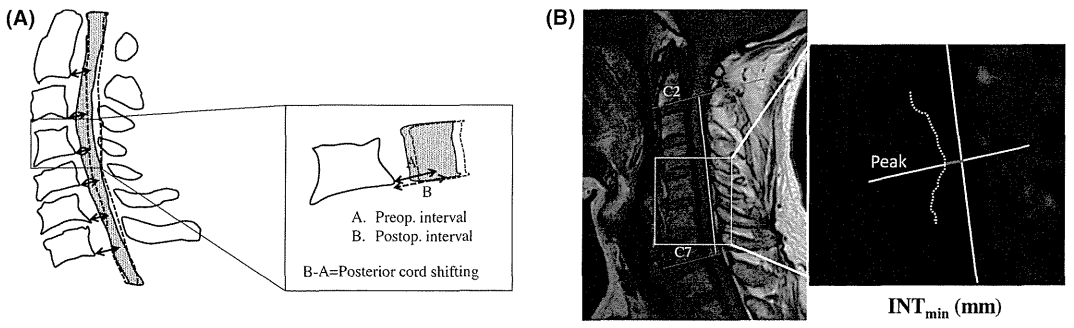


Figure 1. **(A)** Interval between the midpoint of the cord and posterior edge of the anterior element before and after surgery was measured and then the spinal cord shift at each segment was calculated. **(B)** The modified K-line (mK-line) was defined as the line connecting the midpoints of the spinal cord at C2 and C7 on preoperative T1-weighted sagittal magnetic resonance image (left). The minimum interval between the mK-line and the anterior compression factor on the midsagittal image was defined as INT_{min} (right).

TABLE 1. Demographic Data

	Mean ± SD
Age at surgery (yr)	65.3 ± 10.3
Sex (male:female)	34:12
Intervertebral segment responsible	
C3–C4	9
C4–C5	12
C5–C6	19
C6–C7	6
No. of patients	
C3–C7	34
C3–C6	9
C4–C7	3
Pre-JOA score	9.1 ± 2.5
Post-JOA score	12.9 ± 2.6
JOA recovery rate (%)	48.7 ± 26.3
Preoperative C2–C7 lordotic angle (degrees)	15.2 ± 12.2
Preoperative LS angle (degrees)	−0.3 ± 5.8
Preoperative INT_{min} (mm)	5.2 ± 2.3

JOA indicates Japanese Orthopaedic Association; LS, local segmental; INT_{min}, minimum interval between the tip of local kyphosis and a line connecting the midpoint of the cord at the level of the inferior endplates of C2 and C7.

(SPSS Institute, Chicago, IL). In this study, the occurrence of ACS after LAMP was used as a dependent variable, with age, sex, preoperative JOA score, cervical global alignment (C2–C7 lordotic angle), preoperative LS angle, and INT_{min} as independent variables. Sensitivity, specificity, and the receiver operating characteristic curve were measured to evaluate the most valuable index for predicting postoperative ACS.

Furthermore, Spearman correlation coefficient was used to investigate whether INT_{min} was correlated with LS angle or C2–C7 lordotic angle. All data are expressed as the mean ± standard deviation (SD). A P value of less than 0.05 was considered to indicate a statistically significant difference.

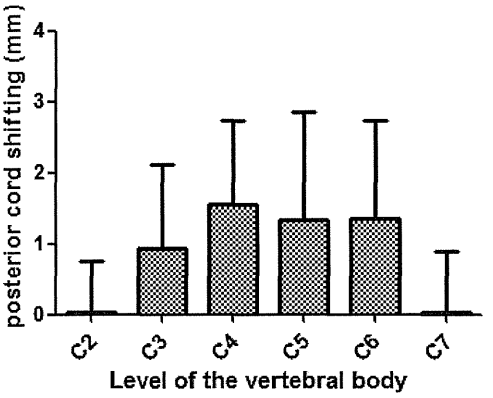


Figure 2. The midpoints of the spinal cord at C2 and C7 did not shift posteriorly even after laminoplasty.

RESULTS

Patient demographic data are shown in Table 1. The mean patient age was 65.3 years (range, 45–82). The intervertebral segment that was closest to the mK-line was C3–C4 in 9 cases, C4–C5 in 12 cases, C5–C6 in 19 cases, and C6–C7 in 6 cases, respectively. The decompression was performed from C3 to C7 in 34 patients, from C3 to C6 in 9 patients, and from C4 to C7 in 3 patients. The mean JOA score before surgery was 9.1 points (range, 3.5–13.5). The average C2–C7 lordotic angle was 15.2° of lordosis (range, 17.3° of kyphosis to 37.1° of lordosis) and the mean LS angle was 0.3° of kyphosis (range, 10.6° of kyphosis to 11.3° of lordosis) before surgery.

Clinical and Radiographical Demographics

Mean JOA score at final visit was 12.9 points (range, 6.5–16.5), yielding a mean JOA score RR of 48.7% (range, 0–94.4). None of the patients had a worse neurological outcome after surgery.

Before checking for a relationship between the mK-line and the occurrence of ACS, a posterior shift of the spinal cord at each level after LAMP was preliminarily measured (Figure 1A). The midpoints of the spinal cord at C2 and C7 did not shift posteriorly even after LAMP (Figure 2). This result suggests that the mK-line can act as an index of the postoperative spinal cord's territory.

On postoperative MRI, we found that 10 patients (21.7%) had postoperative ACS. With regard to a relationship between

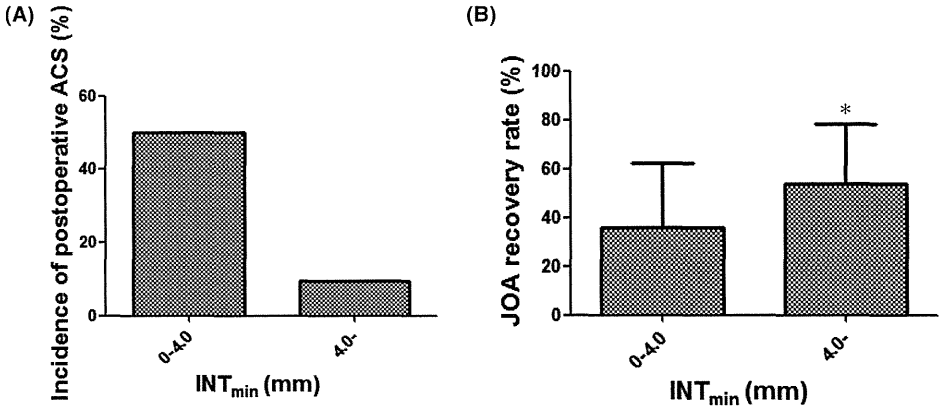


Figure 3. **(A)** The incidence of postoperative ACS was 50% in patients with an INT_{min} of less than 4 mm and 9.4% in those with an INT_{min} of 4 mm or more. **(B)** The Japanese Orthopaedic Association score recovery rate was statistically lower in the patients with an INT_{min} of less than 4 mm than in the patients with an INT_{min} of 4 mm or more ACS indicates anterior compression of the spinal cord. (*$P < 0.05$).

TABLE 2. Predictive Probability of the Incidence of Postoperative Anterior Compression of the Spinal Cord

INT_{min} (mm)	Probability Rate of Postoperative ACS (%)
0	86.7
1	76.0
2	60.6
3	42.8
4	26.6
5	15.0
6	7.9
10	0.5

INT_{min} indicates minimum interval between the tip of local kyphosis and a line connecting the midpoint of the cord at the level of the inferior endplates of C2 and C7.

ACS indicates anterior compression of the spinal cord.

INT_{min} and postoperative ACS in this series, incidence of ACS was 50% in patients with an INT_{min} of less than 4 mm and 9.4% in those with an INT_{min} of 4 mm or more (Figure 3A). Moreover, we also investigated how INT_{min} influenced the JOA score RR. The mean RR was 36.1% in patients with an INT_{min} of less than 4 mm and 53.9% in those with an INT_{min} of 4 mm or more (Figure 3B). There were statistically significant differences between these arms in terms of both the incidence of postoperative ACS and the RR.

Logistic Regression Model Analyzing Risk Factor of Postoperative ACS

Univariate logistic regression showed that only INT_{min} was a significant factor for the occurrence of postoperative ACS. With forward stepwise logistic regression, only INT_{min} (odds ratio: 0.485; 95% confidence interval: 0.290–0.812, $P = 0.02$) was a crucial risk factor for the occurrence of postoperative ACS. The probability of postoperative ACS for each patient was calculated by the following equation: $P = \exp Z/(1 + \exp Z)$; $(Z = 1.878 - 0.723 \times INT_{min})$ (Table 2). Moreover, receiver operating characteristic curve analysis showed an area under the curve of 0.871 (95% confidence interval: 0.767–0.975, $P = 0.0004$). A cutoff of 4.0 mm was associated with 80% sensitivity and 80.6% specificity for predicting postoperative ACS.

Spearman Correlation Coefficient Analysis

We investigated to what degree INT_{min} was correlated with preoperative alignment, including LS angle and C2–C7 lordotic angle. Although the value of INT_{min} was correlated to preoperative LS angle ($Y = 1.078x - 5.883$; $R = 0.475$; $P = 0.001$) (Figure 4A), there was no correlation between INT_{min} and preoperative cervical global alignment (Figure 4B).

Case Presentation

A 67-year-old woman presented with bilateral hand numbness and gait disturbance. Sagittal view preoperative MR image showed that both anterior and posterior factors at the C4–C5 and C5–C6 levels were related to severe stenosis (Figure 5A). Although she received LAMP for multisegmental stenosis, postoperative ACS existed at the C5–C6 level on MR image (Figure 5B). Her persistent numbness of both upper extremities remained even after surgery. Because preoperative INT_{min} was 0.9 mm, the probability of postoperative ACS was 77% according to the abovementioned equation; retrospectively, an anterior procedure or posterior decompression with corrective fusion should have been applied in this case.

DISCUSSION

LAMP has been reported to produce stable long-term neurological improvement for CSM, with benefits potentially lasting more than 10 years.[17] However, it has also been documented that residual anterior compression can lead to unsatisfactory clinical outcomes after LAMP.[7] Sodeyama *et al*[10] reported that posterior cord shift of more than 3 mm leads to good clinical outcomes, showing that an indirect decompression, as well as direct decompression after LAMP, is important for the treatment of compressive lesions. To obtain an indirect decompressive effect, the development of a promising index would be indispensable to evaluating whether postoperative ACS can be prevented after LAMP. Fujiyoshi *et al*[14] developed the K-line on neutral lateral radiograph and reported that patients with OPLL in whom anterior compression of OPLL exceeds the K-line, that is, K-line (−), were likely to have unsatisfactory outcomes. Given that the original K-line would be used to predict postoperative ACS in patients with CSM, however, it is not easy to detect the anterior compression factor such as disc budging and intervertebral spur formation in these patients because it often cannot be observed on plain radiograph. Furthermore, because patients with CSM categorized as K-line (−) are extremely rare (except for patients with excessive global kyphosis) compared with

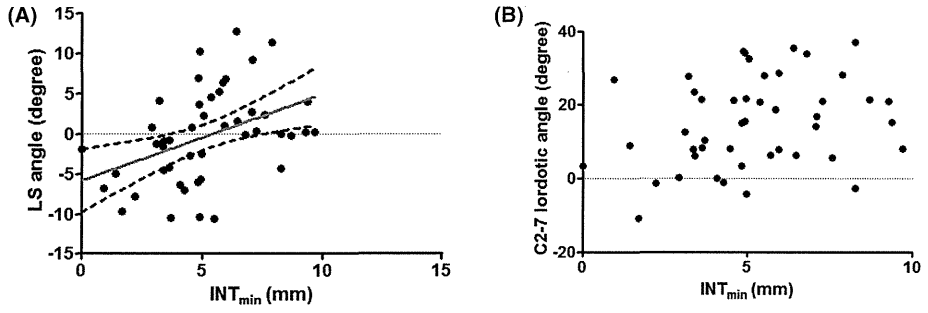
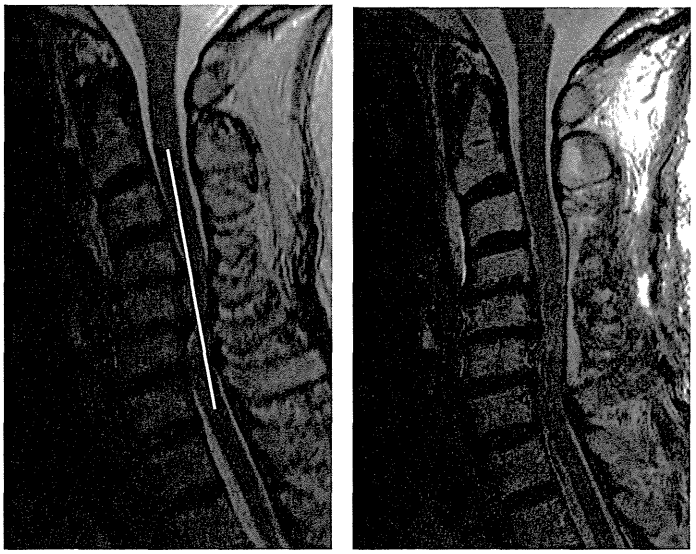


Figure 4. The correlation between INT_{min} and preoperative radiological findings. **(A)** LS angle ($Y = 1.078x - 5.883$; $R = 0.475$; $P = 0.0008$). **(B)** C2–C7 lordotic angle. The value of INT_{min} correlated to preoperative LS angle but not to preoperative C2–C7 lordotic angle. LS indicates local segmental.



(A) (B)

Figure 5. Preoperative magnetic resonance (MR) image shows severe compression of the cervical spinal cord at C4–C5 and C5–C6, and INT_{min} was 0.9 mm at the C5–C6 level **(A)**. Postoperative MR image 6 months after C3–C7 laminoplasty shows insufficient posterior shift of the cord and persistent anterior impingement of the cord at the C5–C6 level **(B)**.

patients with OPLL, we thought that a new criterion should be determined to predict the occurrence of postoperative ACS after posterior decompression. Therefore, as a more reliable index, we selected a line connecting both midpoints of the spinal cord at C2 and C7 on preoperative MRI, as these are points that do not change even after LAMP, and quantified the interval between that line and the anterior compression in patients with CSM to predict insufficient decompression postoperatively.

We analyzed the relationship between preoperative INT_{min} and the incidence of postoperative ACS to assess what values of INT_{min} are best to avoid postoperative ACS. We demonstrated that the occurrence of ACS correlated negatively with preoperative INT_{min}. Indeed, the incidence of ACS was about 50% in patients with an INT_{min} of less than 4 mm, whereas it was 9.4% in those with an INT_{min} of 4 mm or more. Based on the receiver operating characteristic curve, the cutoff value of 4 mm was found to predict postoperative ACS with moderate accuracy. These findings suggest that an INT_{min} of less than 4 mm may be a risk factor for limited posterior cord shift after LAMP. On the contrary, postoperative alignment change may affect newly acquired anterior cord compression. Although we tried to investigate what preoperative factors influenced preoperative alignment change and newly acquired compression, we could not identify any significant predictive factors from the preoperative radiological findings. Because our study involved a small number of patients with postoperative ACS, further study is needed to clarify what preoperative factors accurately predict residual or newly acquired anterior cord compression after LAMP.

In terms of a relationship between radiographical findings and clinical outcomes, there have been many debates.[6,19] Kaptain *et al*[20] and Uchida *et al*[21] have shown that clinical outcome does not usually correlate with preoperative sagittal alignment. Our study was consistent with their findings; preoperative global kyphosis did not affect clinical outcomes in this study (data not shown). Conversely, Suda *et al*[22] calculated with multivariate logistic regression modeling that the maximal preoperative local kyphotic angle possible for successful expansive LAMP is less than 13°. In our study, patients with local kyphosis tended to have smaller INT_{min} values, which correlated with poorer JOA score RR, showing a relationship between unsatisfactory clinical outcome and local kyphosis. Moreover, we found that INT_{min} correlated negatively with the preoperative LS angle of kyphosis, rather than the C2–C7 angle of kyphosis. Therefore, when the surgical method to prevent both the occurrence of ACS and the poor clinical outcome is decided, spine surgeons need to pay attention to the INT_{min} value, which can evaluate the degree of anterior compression including local kyphosis and intervertebral disc bulging.

The limitations of this study include its retrospective nature and relatively small cohort size. Larger, prospective studies are warranted and patients with CSM should be categorized according to cervical sagittal alignment (*i.e.*, straight, kyphosis, and sigmoid types) to clarify whether the INT_{min} value has sufficient predictive value. Furthermore, although our patients were instructed to maintain a neutral position, this was not usually possible while in MRI; however, because all patients followed the same radiographical protocol, the findings may still be considered significant.

In conclusion, ACS after LAMP likely occurs in patients with kyphosis or neutral alignment in which INT_{min} is less than 4 mm; anterior or posterior decompression with fusion would be the most suitable treatment of these patients.

➢ Key Points

- ❑ The midpoints of the spinal cord at C2 and C7 on preoperative midsagittal view MR image did not shift even after LAMP, suggesting that a modified K-line connecting these 2 midpoints can be an index of the spinal cord's postoperative territory.
- ❑ Logistic regression analysis showed that INT_{min} was a significant predictive factor for the occurrence of postoperative ACS.
- ❑ A cutoff point of 4.0 mm is most appropriate for alerting spine surgeons to a high likelihood of postoperative ACS.

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A new alarm point of transcranial electrical stimulation motor evoked potentials for intraoperative spinal cord monitoring: a prospective multicenter study from the Spinal Cord Monitoring Working Group of the Japanese Society for Spine Surgery and Related Research

Clinical article

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Object. Although multimodal intraoperative spinal cord monitoring provides greater accuracy, transcranial electrical stimulation motor evoked potential (TcMEP) monitoring became the gold standard for intraoperative spinal cord monitoring. However, there is no definite alarm point for TcMEPs because a multicenter study is lacking. Thus, based on their experience with 48 true-positive cases (that is, a decrease in potentials followed by a new neurological motor deficit postoperatively) encountered between 2007 and 2009, the authors set a 70% decrease in amplitude as the alarm point for TcMEPs.

Methods. A total of 959 cases of spinal deformity, spinal cord tumor, and ossification of the posterior longitudinal ligament (OPLL) treated between 2010 and 2012 are included in this prospective multicenter study (18 institutions). These institutions are part of the Japanese Society for Spine Surgery and Related Research monitoring working group and the study group on spinal ligament ossification. The authors prospectively analyzed TcMEP variability and pre- and postoperative motor deficits. A 70% decrease in amplitude was designated as the alarm point.

Results. There were only 2 false-negative cases, which occurred during surgery for intramedullary spinal cord tumors. This new alarm criterion provided high sensitivity (95%) and specificity (91%) for intraoperative spinal cord monitoring and favorable accuracy, except in cases of intramedullary spinal cord tumor.

Conclusions. This study is the first prospective multicenter study to investigate the alarm point of TcMEPs. The authors recommend the designation of an alarm point of a 70% decrease in amplitude for routine spinal cord monitoring, particularly during surgery for spinal deformity, OPLL, and extramedullary spinal cord tumor.
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Key Words • **spinal cord monitoring** • **motor evoked potential** • **alarm point** • **technique**

Neurological complications occur in 1.7% of spinal operations, which are among the most frequent surgical complications in Japan.[9] In 2011, the Scoliosis Research Society Morbidity and Mortality Committee reported that the neurological complication

Abbreviations used in this paper: MEP = motor evoked potential; MMT = manual muscle testing; OPLL = ossification of the posterior longitudinal ligament; TcMEP = transcranial electrical stimulation MEP.

rate was 1.3%.[14] The risk of neurological complications during surgery for thoracic ossification of the posterior longitudinal ligament (OPLL) is extremely high; Matsumoto et al.[7] reported that the incidence of neurological complications was 26%. Matsuyama et al.[8] reported a rate of 31% for neurological deterioration after surgery for intramedullary spinal cord tumors. As neurological complications represent one of the most serious complications, care needs to be taken to prevent perioperative neurological injury, particularly regarding spinal OPLL, spinal cord tumor, and scoliosis surgery.

Recent reports have shown that multimodal intraoperative spinal cord monitoring can reduce neurological deterioration and provide increased accuracy in the detection of spinal cord injury.[1,2,17] In particular, transcranial electrical stimulation motor evoked potentials (TcMEPs) are widely used for intraoperative spinal cord monitoring. Monitoring of TcMEPs became the gold standard due to their increased sensitivity and the importance of motor function. However, there is no definite alarm point for TcMEPs because previous alarm points were derived from single-institution studies rather than a multicenter study.

We analyzed 48 true-positive cases (that is, decrease in potentials followed by a new neurological motor deficit postoperatively) experienced between 2007 and 2009 from 18 institutions that are part of the monitoring working group of the Japanese Society for Spine Surgery and Related Research and the study group on spinal ligament ossification. Based on this analysis, we designated a decrease in amplitude of 70% or more as the alarm point. The purpose of the current study was to evaluate a new alarm point for TcMEPs in a prospective multicenter study and to demonstrate that a 70% decrease in amplitude represents a more accurate alarm point than those used previously.

Methods

We performed intraoperative spinal cord monitoring using TcMEPs in 959 patients with spinal deformities, OPLL, and spinal cord tumors between 2010 and 2012. There were 360 cases of spinal cord tumor (38%), 317 cases of OPLL (33%), and 282 cases of spinal deformity (29%). We also included 93 patients with intramedullary spinal cord tumors and 114 patients with thoracic OPLL (Fig. 1).

Monitoring of TcMEPs was performed under uniform monitoring conditions at the 18 hospitals belonging to the Spinal Cord Monitoring Working Group of the Japanese Society for Spine Surgery and Related Research and of the study group on spinal ligament ossification. This study was supported by a Japanese Health Labor Sciences research grant.

Total intravenous anesthesia was administered during intraoperative spinal cord monitoring. The drugs administered were propofol (3–4 μg/ml), fentanyl (2 μg/kg), and vecuronium (0.12–0.16 mg/kg). Anesthesia was maintained using propofol (3 μg/ml), fentanyl (1 μg/kg/hr), and vecuronium (0–0.04 mg/kg/hr) and did not exceed 2/4 train of four.

The transcranial stimulus conditions comprised 5 train stimuli, a stimulus interval of 2 msec, a stimulus of 300–600 V, a filter of 50–1000 Hz, a recording time of 100 msec, and a total of fewer than 20 stimuli. The stimulator was placed 2 cm anterior and 4 cm lateral to Cz (International 10-20 system) over the cerebral cortex motor area.

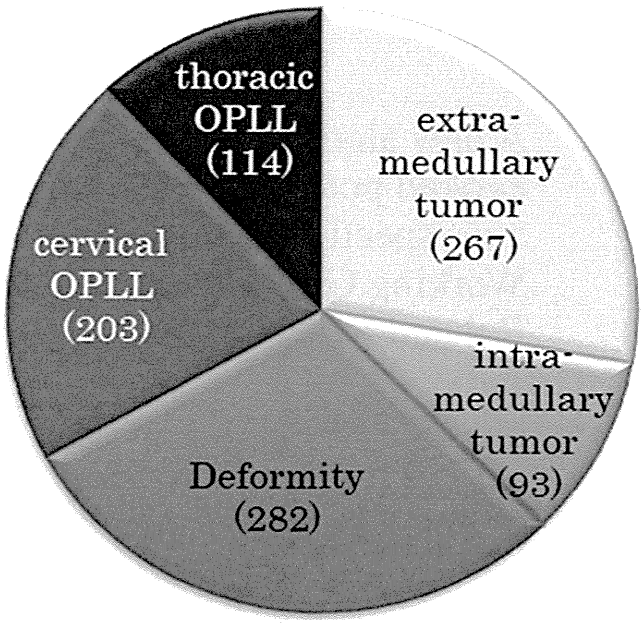

FIG. 1. Pie chart showing the breakdown of diagnoses.

The TcMEPs were recorded from the peripheral limbs via needle or disc electrodes and from the anus via plug-type electrodes. The evoked muscles, depending on the site of surgery, were selected from some or all of the deltoid, biceps, triceps, hypothenar, quadriceps femoris, hamstrings, tibialis anterior, gastrocnemius, and sphincter muscles. We measured the amplitudes of TcMEPs by peak-to-peak voltages. The amplitudes prior to the invasive procedures were regarded as control values.

Our alarm point was designated as a decrease in amplitude of 70% or greater. We set the alarm point based on our retrospective analysis of 48 true-positive cases experienced between 2007 and 2009 from 18 institutions belonging to the monitoring working group of the Japanese Society for Spine Surgery and Related Research. The TcMEPs in these cases showed that we could not predict mild postoperative paralysis (1-grade decrease in the manual muscle testing [MMT] grade). However, all cases with moderate-to-severe postoperative paralysis (2- to 5-grade decrease in MMT grade) exhibited a greater than 70% decrease in TcMEP amplitude at the end of surgery (Fig. 2).

As Kim et al.[4] reported, a true-positive case is defined as a TcMEP alert with a persistent decrease in potentials at the end of the operation, followed by the observation of a new neurological motor deficit after the operation. A false-positive case is defined as an alert with a persistent decrease of potentials at the end of the operation and the absence of any new postoperative deficit. A true-negative case is defined as the absence of any TcMEP alert during surgery and no new postoperative deficits. A false-nega-

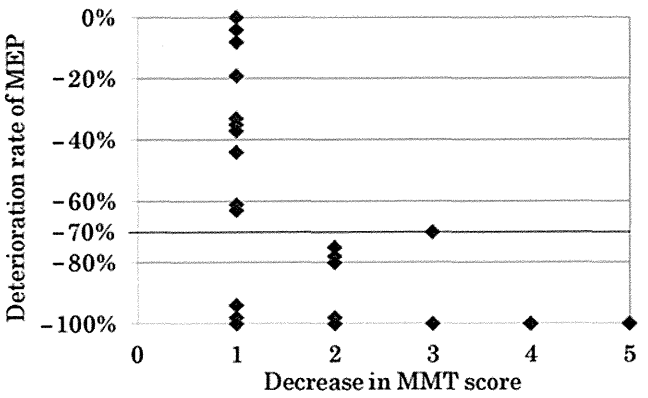

FIG. 2. Retrospective data of 48 cases of postoperative neurological deterioration experienced between 2007 and 2009 from our 18 institutions. All TcMEPs in patients with moderate to severe neurological deterioration decreased more than 70% in amplitude. Thus, we set the alarm point as a greater than 70% decrease in amplitude.

tive case is defined as the absence of an alert in a patient with a new postoperative motor deficit. A TcMEP alert that normalized after corrective measures in a patient who emerged without new motor deficits was defined as indeterminate (rescue case). Variability of the TcMEPs and the pre- and postoperative motor deficit were analyzed prospectively. Informed consent was obtained from all patients.

Results

The TcMEPs yielded 38 true-positive cases, 786 true-negative cases, 78 false-positive cases, and 2 false-negative cases in this study (Fig. 3). The remaining 55 cases were rescue cases. Therefore, the sensitivity was 95%, and the specificity was 91%. The positive predictive value was 32.8%, the negative predictive value was 99.7%, the false-positive rate was 9.0%, and the false-negative rate was 5.0% (Fig. 4). In 55 cases, the TcMEP amplitudes decreased during surgery; however, they recovered at the end of surgery subsequent to steroid injection or release of the scoliosis correction. We regarded these 55 cases as rescue cases; they were excluded from the analysis of accuracy because without a wakeup test we were not convinced that the temporal decrease in amplitude indicated real motor deficit. The patients in the false-negative cases recovered fully from their transient paralysis.

There were 38 true-positive cases that included 15 patients with thoracic OPLL, 7 patients with extramedullary spinal cord tumor, and 7 patients with intramedullary spinal cord tumor (Fig. 5).

The duration of postoperative paralysis was not associated with the degree of decreased amplitude. Twelve of the 38 true-positive cases lost motor evoked potentials (MEPs) completely at the end of the operations, and the patients recovered their motor function within 1 month. Motor deficits lasting more than 3 months occurred in 9 cases of absent response, 2 cases of amplitude decreased by 80%, and 3 cases of amplitude decreased by 70% (Fig. 6).

Both false-negative cases occurred during surgery for cervical intramedullary spinal cord tumors. One of

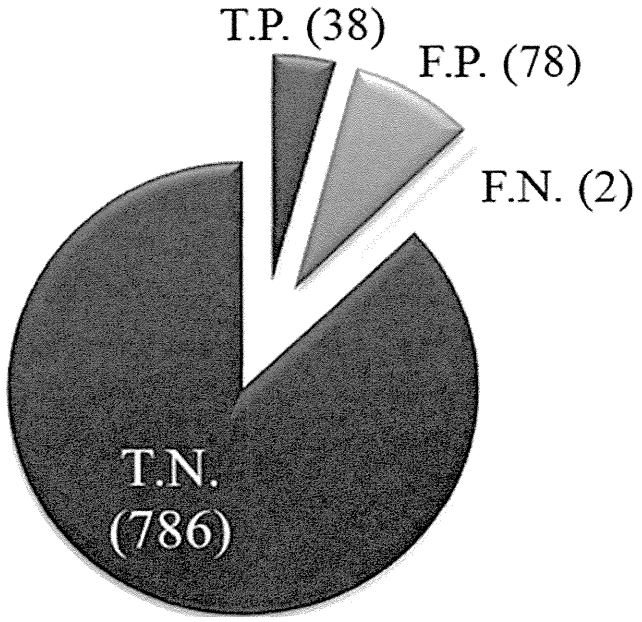

FIG. 3. TcMEP monitoring and clinical results with a criterion of a 70% decrease in amplitude. There were 38 true-positive (T.P.) cases and 2 false-negative (F.N.) cases, which were both intramedullary spinal cord tumors. There were 55 indeterminate cases that were excluded from the analysis of monitoring accuracy. F.P. = false positive; T.N. = true negative.

these patients was paralyzed postoperatively with a 54% decrease in amplitude in the triceps MEPs at the end of surgery. In the other patient, the TcMEP in the tibialis anterior muscle decreased by 52%, and postoperatively the MMT grade in this muscle deteriorated from 4 to 2.

There was one true-positive case in a patient with cervical OPLL; a 75% decrease in amplitude was noted at the end of surgery, and postoperatively the patient's MMT grade worsened from 4 to 0. Regarding this case, the 80% decrease amplitude criterion was unable to predict neurological deterioration after surgery (Fig. 7).

The accuracy of monitoring using a criterion of a 70% decrease in amplitude was high with a sensitivity of 95% and specificity of 91%.

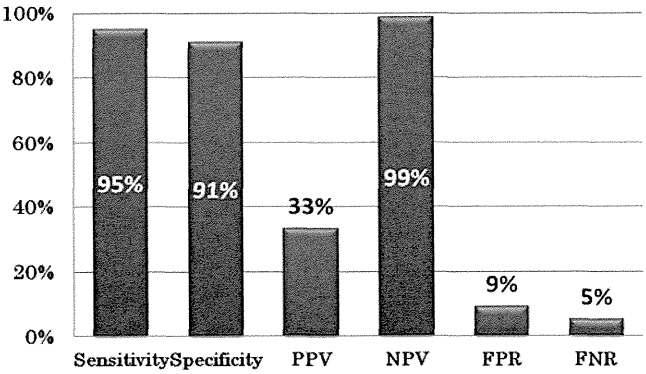

FIG. 4. Accuracy of TcMEP monitoring using a criterion of a 70% decrease in amplitude. FNR = false-negative rate; FPR = false-positive rate; NPV = negative predictive value; PPV = positive predictive value.

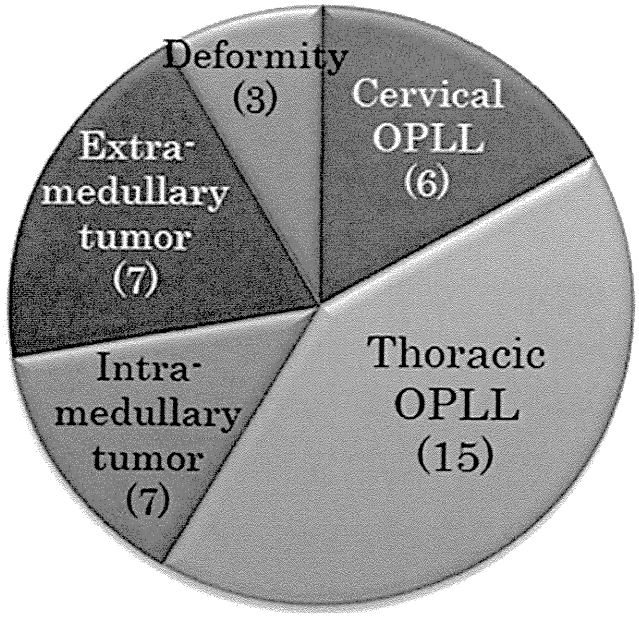

FIG. 5. Distribution of the diagnosis of true-positive cases.

Discussion

Warning criteria for TcMEPs are not well established because no previous prospective multicenter study has been published. Most reports have used a criterion of a 50%–80% decrease in amplitude,[5,6,10,11,13] but some reports used complete loss of response[10,12] or morphological change.[7,13] Intraoperative spinal cord monitoring has been used for various spinal diseases. The 70% decrease in amplitude criterion in our study yielded a higher accuracy for neurological deterioration after spinal cord tumor, deformity, and OPLL surgery.

As a historical cohort, Raynor et al.[13] reported a 25-year experience of intraoperative spinal cord monitoring in 12,375 spinal surgeries. They described 386 monitoring alerts and 14 cases of permanent neurological deterioration when they used threshold criterion. Therefore, their study reported more alerts and fewer cases of neurological deterioration than ours (Table 1).

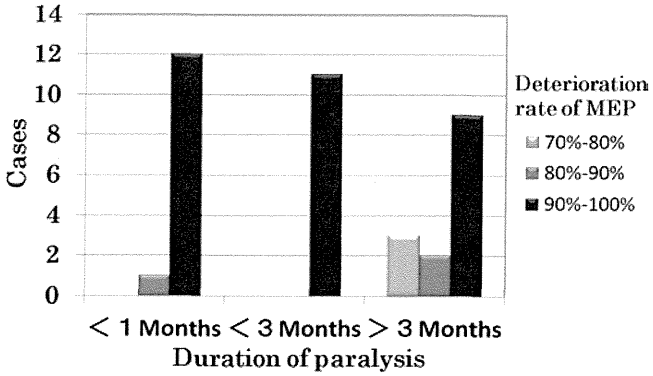

FIG. 6. The relationship between the decreased degree of amplitude and the duration of postoperative paralysis. There was no relationship observed between the percentage of decreased amplitude and months of paralysis.

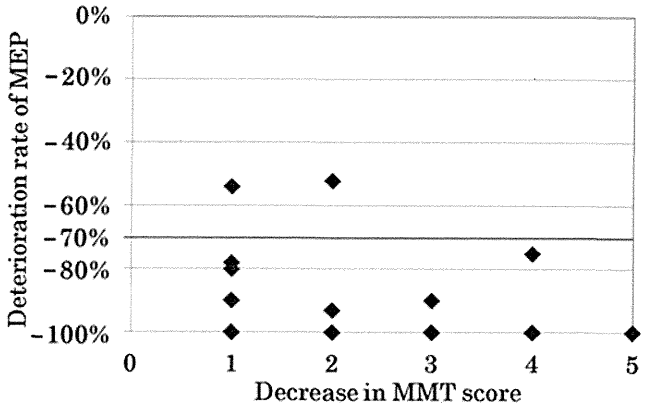

FIG. 7. The distribution plot of the decrease in MMT score with the deterioration rate of MEP. The 2 plots above 70% decrease in amplitude represent false-negative cases.

Park et al.[10] reported a 50% amplitude criterion in 29 cervical kyphosis surgeries. The TcMEPs yielded a sensitivity of 75% and a specificity of 84%. Lee et al.[6] reported a 60% amplitude criterion in 1445 anterior cervical surgeries. There were 267 TcMEP alerts (18.4%) and only 2 neurological deficits. We thought that a criterion of a 50%–60% decrease in amplitude provided an excess of alarms and reduced specificity.

Langeloo et al.[5] reported on 145 patients with spinal deformity who underwent corrective surgery with TcMEP monitoring. The alarm point was designated as a response amplitude decrease of more than 80% that resulted in 16 TcMEP alerts and only 5 neurological deficits, a sensitivity of 100%, and a specificity of 91%. They reported a reduced incidence in postoperative neurological deterioration. In our study, we observed 171 TcMEP alerts and 40 cases of neurological deterioration. One patient with cervical OPLL exhibited a postoperative decrease in TcMEP amplitude of 75% with severe neurological deterioration postoperatively (MMT grade from 4 to 0). In our retrospective study from 2007 to 2009 we also observed 4 patients who exhibited a 70%–80% decrease in TcMEP amplitude and who had moderate postoperative neurological deterioration. These cases suggested that the 80% amplitude criteria exhibited reduced sensitivity compared with the 70% amplitude criterion. These cases supported high validity of the 70% amplitude criterion. The criterion of a 70% decrease in amplitude was useful for predicting neurological injury, and we could avoid neurological complications based on TcMEPs.

Sala et al.[16] reported that TcMEP disappearance was a reason to modify intramedullary spinal cord tumor surgery, but a 50% D-wave amplitude decrease was the major indication to stop surgery. We observed 16 patients with neurological deterioration of more than 2 grades in MMT in whom TcMEPs disappeared entirely. Our study suggests that a complete loss of response indicates mild to severe paralysis; thus, loss of response is too late to alarm.

There were 78 false-positive cases in our study. According to other studies,[2,6,17] the definition of false-positive was based on neurological "events." However, our definition of false-positive was based on neurological de-

TABLE 1: Literature review of TcMEP alarm points*

Authors & Year	Diagnosis	TcMEP Criterion	Other Modality	No. of Cases	Monitoring Alerts	Neurological Deterioration	Precision (%)
Pelosi et al., 2002	deformity	50%	SSEP	126	16	1	6
Langeloo et al., 2003	deformity	80%		132	16	3	19
Quiñones-Hinojosa et al., 2005	SCT	waveform		28	13	12	92
Lee et al., 2006	cervical pathology	60%, 10% latency	SSEP	1445	67	2	3
Kim et al., 2007	cervical pathology	80%	SSEP	52	6	1	17
Sutter et al., 2007	SCT	50%, 10% latency		109	25	4	16
Park et al., 2011	deformity	50%, 10% latency	SSEP, EMG	29	7	4	57
Ito et al., 2012	spinal pathology	waveform	SSEP, D-wave	295	67	8	12
Raynor et al., 2013	spinal pathology	threshold	SSEP, EMG	12,375	386	14	4
present study	OPLL, deformity, SCT	70%		959	116	40	35

* EMG = electromyography; SCT = spinal cord tumor; SSEP = somatosensory evoked potential.

terioration. The "true" true-positive rate (number of neurological deterioration cases/number of monitoring alert cases) in our study was higher than that in other reports. Thus, we thought that the "true" false-positive rate was less than that reported in other articles, and specificity changed greatly by the definition.

Two false-negative cases showed a decreased TcMEP amplitude of approximately 50%. Clinically, the patients' paralysis recovered 1 month after surgery, and the patients had no trouble with daily life.

In the event of TcMEP alert, we tried to recover spinal cord function through suspension of the surgery or administration of steroids or antihydropic agents. Releasing the correction was recommended in surgery for spinal deformity. Our study observed 172 cases of TcMEP alerts and 55 cases of TcMEPs recovered after treatment for spinal cord injury without postoperative motor deterioration. These 55 indeterminate cases are important for the meaningful monitoring of "rescue" cases.

The limitation of this study was that it was a prospective study. Thus, we could not retrospectively evaluate 50% or 80% amplitude criteria or other alarm criteria in this series. We included 3 different types of spinal pathology as a whole. Both false-negative cases occurred during surgery for intramedullary spinal tumors. Intramedullary spinal tumor surgery is associated with a risk of selective spinal cord injury. It may be more difficult to detect selective spinal cord injury than whole spinal cord injury. Based on one false-negative case that resulted in transient paralysis of the patient's triceps muscle, we speculated that there are differences in alarm points between segmental spinal cord injury and spinal tract injury.[15] Further investigation might reveal the differences in the alarm points for spinal pathology and the site of intraoperative spinal cord injury.

Our TcMEP monitoring using the 70% amplitude criterion provided increased sensitivity (95%) and specificity (91%) during monitoring of severe spinal diseases of spinal cord tumor, deformity, and OPLL. In addition, there were 55 rescue cases that indicated favorable results of intraoperative spinal cord monitoring.

Conclusions

The new criterion of a 70% decrease in amplitude of TcMEPs provided increased sensitivity (95%) and specificity (91%) for intraoperative spinal cord monitoring. Thus, a 70% decrease in amplitude was the ideal TcMEP alarm point, except in cases of intramedullary spinal cord tumor. We recommend this alarm point for routine spinal cord monitoring, particularly for surgery treating spinal deformities, extramedullary spinal cord tumors, and OPLLs.

Disclosure

Federal funds from 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 to the subject of this manuscript.

Author contributions to the study and manuscript preparation include the following. Conception and design: Matsuyama. Acquisition of data: Kobayashi, Kawabata, Ando, Kanchiku, Saito, Takahashi, Ito, Muramoto, Fujiwara, Kida, Yamada, Wada, Yamamoto. Analysis and interpretation of data: Kobayashi, Shinomiya, Kawabata, Ando, Kanchiku, Saito, Takahashi, Ito, Muramoto, Fujiwara, Kida, Yamada, Wada, Yamamoto. Drafting the article: Kobayashi. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kobayashi. Study supervision: Matsuyama, Shinomiya, Satomi, Tani.

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Research article

Treatment with basic fibroblast growth factor-incorporated gelatin hydrogel does not exacerbate mechanical allodynia after spinal cord contusion injury in rats

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Besides stimulating angiogenesis or cell survival, basic fibroblast growth factor (bFGF) has the potential for protecting neurons in the injured spinal cord.

Objective: To investigate the effects of a sustained-release system of bFGF from gelatin hydrogel (GH) in a rat spinal cord contusion model.

Methods: Adult female Sprague–Dawley rats were subjected to a spinal cord contusion injury at the T10 vertebral level using an IH impactor (200 kdyn). One week after contusion, GH containing bFGF (20 μg) was injected into the lesion epicenter (bFGF – GH group). The GH-only group was designated as the control. Locomotor recovery was assessed over 9 weeks by Basso, Beattie, Bresnahan rating scale, along with inclined plane and Rota-rod testing. Sensory abnormalities in the hind paws of all the rats were evaluated at 5, 7, and 9 weeks.

Results: There were no significant differences in any of the motor assessments at any time point between the bFGF – GH group and the control GH group. The control GH group showed significantly more mechanical allodynia than did the group prior to injury. In contrast, the bFGF – GH group showed no statistically significant changes of mechanical withdrawal thresholds compared with pre-injury.

Conclusion: Our findings suggest that bFGF-incorporated GH could have therapeutic potential for alleviating mechanical allodynia following spinal cord injury.

Keywords: Allodynia, Basic fibroblast growth factor, Scaffold, Spinal cord injuries, Motor deficits, Neuroprotection, Locomotor recovery, Paraplegia

Introduction

Spinal cord injury (SCI) is the most devastating type of trauma for patients due to the long-lasting disability and limited responses to acute drug administration and efforts at rehabilitation. Previously, we reported on combinational therapy, bone marrow stromal cell (BMSC) transplantation, and Rho-kinase inhibitor administration for spinal cord contusion.[1] Combination therapy showed better recovery than controls, but we detected no synergy between the components of the combination. We counted lower numbers of remaining BMSCs and saw a gradual decrease in the number of BMSCs over the observation period. We hypothesized that we might have observed more locomotor recovery had the remaining cells been more abundant.

Gelatin hydrogel (GH) incorporating basic fibroblast growth factor (bFGF) is one of the more promising tools for treating SCI. bFGF-incorporated GH has enhanced angiogenesis in several experimental models,[2–4] and it has already found some clinical

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usage, including a phase I/IIa study in humans in the hope of enhancing angiogenesis.[5] Multiple studies have also identified various functions for bFGF itself in damaged central nerve system tissue, including the following: attenuating neurotoxicity and increasing antioxidant enzyme activities in hippocampal neurons;[6] protecting against excitotoxicity and chemical hypoxia in both neonatal and adult rat neurons;[7] preventing the death of lesioned cholinergic neurons *in vivo*;[8] and protecting spinal motor neurons after experimental SCI.[9] These research findings together suggest that bFGF-incorporated GH has the potential for saving damaged neuronal cells and improving angiogenesis after SCI.

BMSC with fibrin scaffolding has been observed to improve survival of transplanted cells after spinal cord hemisection.[10] The combination of the neurotrophin-3, platelet-derived growth factor, and fibrin scaffold has been reported to enhance the total number of neural progenitor cells present in the spinal cord lesion 2 weeks after injury.[11] The study findings together suggest that the controlled release of growth factor incorporated into a scaffold in conjunction with cell transplantation has the potential to improve the survival of transplanted cells and enhancing locomotor recovery after SCI.

In the present study, we sought to establish the safety of bFGF-incorporated GH in humans. Our study protocol was to inject bFGF-incorporated GH and GH without bFGF into contused spinal cords in rats and to measure locomotion for 9 weeks after SCI, as well to estimate two types of allodynia before and after SCI.

Methods

Experimental groups

The 18 animal subjects were randomly assigned to two groups: (1) the bFGF + GH group (bFGF – GH, $n = 8$), which received an injection of bFGF + GH mixture into the spinal cord; (2) the GH-only group (GH, $n = 10$), which received an injection of GH without bFGF into the spinal cord.

bFGF-incorporated GH treatment

bFGF-incorporated GH

A frozen aliquot of bFGF (10 μg/μl) was diluted 1:1 with phosphate-buffered saline (PBS) and incubated overnight at 4°C (5 μg/μl). GH (2 mg) was mixed with a 20-μl aliquot of bFGF and incubated at 37°C for 1 hour. Just before injection, bFGF-incorporated GH was diluted by 20 μl of PBS. We injected 8 μl bFGF-incorporated GH into the injured spinal cord.

Animal surgery

Our experimental SCI protocol utilized a total of 18 8-week-old female Sprague–Dawley rats (SLC, Hamamatsu, Japan). Rats were anesthetized with 1.6% halothane in 0.5 l/minute oxygen. We performed a laminectomy at the T9–T10 levels and induced a contusion injury of the spinal cord with the infinite horizon impactor (IH impactor, 200 kdyn, Precision Systems and Instrumentation, Lexington, NY, USA). Rats were group-housed in the animal facility and maintained under conditions of constant temperature and humidity. Food and water were provided *ad libitum*. Manual bladder expression was performed twice a day until recovery of the bladder reflex. All animals were given antibiotics (500 μl/day; Bactramin, Chugai Pharmaceutical, Tokyo, Japan) by subcutaneous administration once a day for 3 days. Body weight after SCI was measured weekly, from which we calculated body weight ratios by dividing each post-injury body weight by the body weight before surgery.

Seven days after injury, we re-exposed the injury site and injected the same volume (8 μl) of bFGF-incorporated GH, or GH only, into the center of the injured spinal cord using a micro-glass pipette needle attached to a 10-μl Hamilton syringe (Hamilton Company, Reno, NV, USA) under microscopy. We performed the injection at multiple depths (2, 1.5, 1.0, and 0.5 mm) during drawback, and the needle was left in the spinal cord for 3 minutes following the last injection in order to minimize reflux. None of the animals showed abnormal behavior. All the experimental procedures were performed in compliance with the guidelines established by the Animal Care and Use Committee of Chiba University.

Assessments of sensory motor functions

Basso, Beattie, Bresnahan open field locomotor test

Hind limb function was assessed in an open field (100 cm × 60 cm plastic pool) using the Basso, Beattie, Bresnahan (BBB) open field locomotor test.[12] Measurements were performed weekly thereafter for 9 weeks. Tests were videotaped for 5 minutes and scored by a trained observer who was unaware of the treatment group to which each subject was assigned.

Inclined plane test

Each animal was placed in head-up, transverse, and head-down positions on an inclined plane and the angle of slope gradually increased. The angle at which the animal fell down from the slope was recorded for each position, two trials per animal, after SCI. The better of the two trial results for each subject were

combined and compared among the three groups. We performed these measurements before surgery and then 4, 6, and 8 weeks after SCI.

Rota-rod test

Four and 6 weeks after SCI, animals were placed on a 5 cm-wide turning cylinder (Rota-rod MK-630B, Muromachi Kikai, Japan) and forced to walk on it. The speed of rotation was gradually accelerated from 3 rpm (rotations per minute) to 30 rpm, and then maintained at 30 rpm for 5 minutes (Mode A1, 3–30 rpm). The time when the animal fell from the Rota-rod was recorded. Preoperatively, animals were able to stay on the Rota-rod for a mean duration of 199.3 seconds.

Sensory tests

Thermal nociceptive thresholds in rat hind limbs were evaluated using a Hargreaves device (Ugo Basile, Varese, Italy). The rats were placed in individual transparent acrylic boxes with the floor maintained at 28°C. A heat stimulus (150 mcal/seconds/cm^2) was delivered using a 0.5 cm-diameter radiant heat source positioned under the plantar surface of the hind limb. The heat source was placed alternately under each hind limb to avoid anticipation by the animal. A cutoff time of 22 seconds was used, as we had previously ascertained that no tissue damage would result within this time period. The withdrawal threshold was calculated as the average value of three consecutive tests. Mechanical withdrawal thresholds in rat hind limbs were tested using a dynamic plantar aesthesiometer (Ugo Basile), in which a mechanical stimulus was applied via an actuator filament (0.5 mm diameter), which under computer control applied a linear ramp 5.0 g/seconds to the plantar surface of the hind limb. The withdrawal threshold was calculated as the average of six consecutive tests. Both tests were performed pre-injury and then 5, 7, and 9 weeks after contusion.

Anterograde labeling of the cortico-spinal tract with biotinylated dextran amine; immunohistochemical; and histological assessments

Nine weeks after contusion, the cortico-spinal tract was bilaterally traced under halothane anesthesia with 2.0 µl biotinylated dextran amine (BDA, molecular weight: 10 000, 10% in 0.01 M PBS, Molecular Probes, Carlsbad, CA). A micro-glass pipette needle attached to a 2-µl Hamilton syringe was stereotaxically guided, and BDA was slowly injected into four sites in the sensorimotor cortex for the hind limb at a 1-mm depth: Bregma 2 mm, sagittal suture 2 mm; Bregma 2 mm, sagittal suture 3 mm; Bregma 2.5 mm, sagittal suture 3 mm; Bregma 2.5 mm, sagittal suture 2.5 mm. The needle was left in place for 1 minute following each injection to minimize reflux.

Histology

Animals were subjected to trans-cardiac perfusion with 4% paraformaldehyde in PBS (pH 7.4) 14 days after BDA injection. The spinal cords were dissected and immersed overnight in 4% paraformaldehyde and then stored in 20% sucrose in PBS. The spinal cords were cut into 20-mm lengths (10 mm rostral to and 10 mm caudal to the lesion site) and embedded in optimal cutting temperature (OCT) compound (Tissue Tek, Sakura Finetechnical, Tokyo, Japan). We sectioned each block in the sagittal plane (25 µm) using a cryostat and mounted eight consecutive sections on poly-L-lysine-coated slides (Matsunami, Tokyo, Japan) to make serial sections. The sections on each slide were sliced at 150 µm intervals; each eight section slide therefore covered approximately 1200 µm of the lesion site. We performed histological or immunohistochemical staining on the slides.

To evaluate lesion size, we stained three slices from each animal with cresyl violet. We determined the cavity size of each section using Photoshop 5.5 software (Adobe, San Jose, CA, USA). We calculated a mean cavity size from these three values for each animal and compared cavity sizes between groups.

For anterograde labeling of the cortico-spinal tract with BDA, sections were incubated with Alexa Fluor 594-conjugated streptavidin (1:800; Molecular Probes). We selected seven consecutive sections from the rostral edge of the lesion center, which we photographed with a 20× objective lens using a fluorescence microscope (DP71, Olympus, Tokyo, Japan). We added up the number of fibers and compared the fiber counts between the groups.

Three slices per animal, centered on the lesion epicenter, were incubated with rabbit anti-calcitonin gene-related peptide (CGRP) antibody (1:1000, ImmunoStar, Inc. Hudson, WI, USA) or rabbit anti-von Willebrand factor (1:400, Dako Cytomation, Glostrup, Denmark), then reacted with Alexa-Fluor 594 goat anti-rabbit IgG secondary antibody. Slices were photographed on the rostral and caudal edges of the lesion epicenter with a 10× objective lens using a fluorescence microscope (DP71, Olympus). The numbers of CGRP-positive immunoreactive fibers or von Willebrand factor-positive immunoreactive vessels were counted and averaged.

Statistical analysis

For histological studies and for assessments of sensory motor functions at each time point, we performed a

Mann–Whitney *U* test. For the 9-week locomotor scale, we performed repeated-measures analysis of variance (ANOVA). Data were reported as mean values ± SEM. Differences with *P* values <0.05 were considered statistically significant.

Results

We measured body weight ratios every week after SCI. Rats were treated with bFGF – GH, or GH, 7 days after SCI. Weight loss was severe at 7 days after SCI: weight loss ratios for the bFGF – GH and the GH groups were 0.958 ± 0.020 and 0.938 ± 0.013, respectively. At the end of 9 weeks, the weights of the animals had increased to 1.322 ± 0.039 and 1.319 ± 0.034, respectively, for two groups. No statistically significant increase in the body weight ratio was observed during the entire experiment.

BBB locomotor scores 7 days after SCI were 1.0 ± 0.49 and 0.6 ± 0.34, respectively, for the bFGF – GH and the GH groups, and the intergroup difference was not statistically significant. BBB scores at 9 weeks were 10.5 ± 0.54 and 10.2 ± 0.58, respectively, for the two groups, and again no statistically significant difference between the groups was observed (Fig. 1). Repeated-measures ANOVA also failed to detect any statistically significant intergroup differences in BBB scores over the entire experiment period ($P = 0.27$).

Inclined plane testing showed that before SCI, rats could keep their body on an inclined plane at 61.04 ± 0.43° in a head-up position, 57.29 ± 0.44° in a transverse position, and 45.83 ± 0.25° in a head-down position. The differences were not statistically significant between groups at 4, 6, and 8 weeks after SCI (data not shown). The Rota-rod test also showed no statistically significant differences between groups at 4, 6, and 8 weeks after SCI (data not shown).

Analysis of the pre-injury data for the Hargreaves device revealed a mean thermal latency of 16.9 ± 0.4 seconds ($n = 18$). Thermal latency decreased to mean values of 13.5 ± 0.9 seconds at 5 weeks, 14.7 ± 1.0 seconds at 7 weeks, and 14.0 ± 1.1 seconds at 9 weeks in the bFGF – GH group, and 13.2 ± 1.0 seconds at 5 weeks, 13.9 ± 0.9 seconds at 7 weeks, and 13.4 ± 0.7 seconds at 9 weeks in the GH group. Although thermal latency decreased in both groups after SCI compared with normal pre-injury rats, the differences did not reach statistical significance. In addition, none of the differences in mean thermal latency between the groups at any time period were statistically significant.

Mechanical thresholds using a dynamic plantar aesthesiometer had a mean pre-injury value of 31.5 ± 1.4 g (Fig. 2: $n = 18$). The mean values decreased to 26.2 ± 1.5 g at 5 weeks, 27.2 ± 1.2 g at 7 weeks, and 28.5 ± 1.9 g at 9 weeks in the bFGF – GH group, and 22.9 ± 2.1 g at 5 weeks, 25.2 ± 2.0 g at 7 weeks, and 28.5 ± 2.2 g at 9 weeks in the GH group. The GH group exhibited significantly more mechanical allodynia compared with pre-injury rats at 5 and 7 weeks ($P = 0.006$ and $P = 0.021$, respectively). The decreases in mechanical thresholds in the bFGF – GH group were not statistically significant over the course of the entire experiment.

To elucidate the efficacy of bFGF–GH or GH for tissue protection or tissue sparing after SCI, we measured the area of the cystic cavity with cresyl violet staining 9 weeks after injury (Fig. 3). The differences between the groups did not reach statistical significance (Fig. 3C, $P = 0.94$).

The BDA signals rostral to the lesion epicenter were 49.1 ± 13.7 and 38.9 ± 11.9 for the bFGF–GH and GH groups, respectively (Fig. 4). The differences

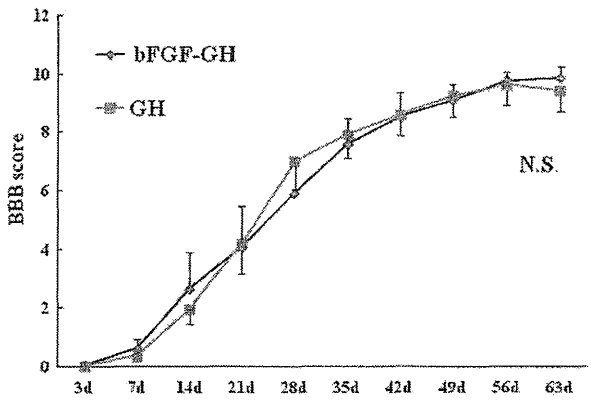

Figure 1 BBB locomotor scores during the first 9 weeks after SCI. The differences between the groups were not statistically significant ($P = 0.27$).

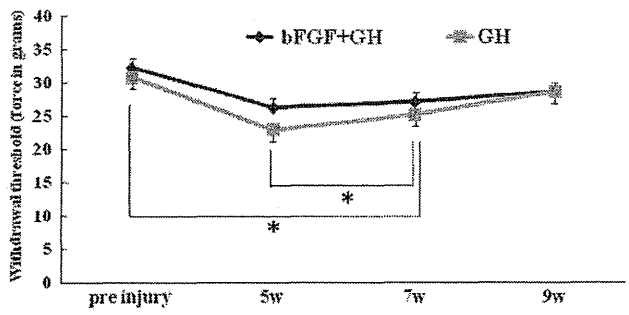

Figure 2 Mechanical thresholds using a dynamic plantar aesthesiometer were performed pre-injury and also 5, 7, and 9 weeks after contusion. The GH group showed significantly more mechanical allodynia compared with pre-injury rats at 5 and 7 weeks ($P = 0.006$ and $P = 0.021$, respectively). However, the bFGF – GH group showed no statistically significant decrease over the entire experiment.

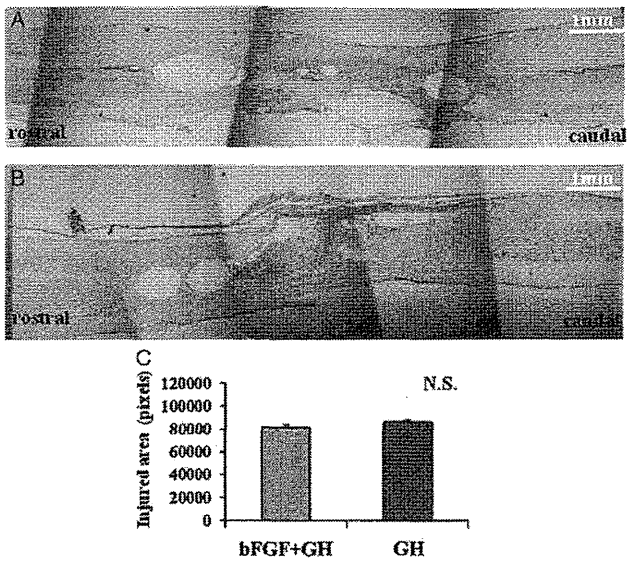

Figure 3 Cresyl violet staining 9 weeks after SCI did not show statistically significant cavity size differences between the two groups. The cavity size of each section was analyzed. Representative figures of each group from the bFGF + GH group (A) and the GH group (B) are presented. The differences among groups did not reach statistical significance (C, $P = 0.94$). Bar = 1 mm for figures A, B.

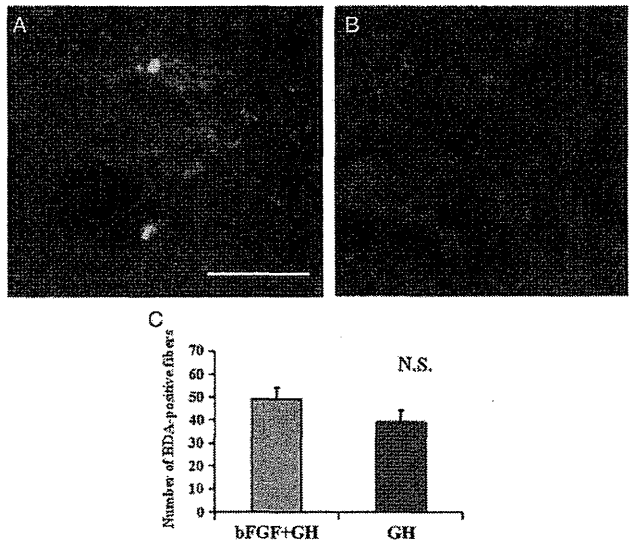

Figure 4 Biotinylated dextran amine tracing 8 weeks after SCI. The BDA signals at the rostral edge of the lesion epicenter were analyzed. The differences between the groups did not reach statistical significance (C, $P = 0.22$). Bar = 100 μm for figures A, B.

between the two groups did not reach statistical significance (Fig. 4C, $P = 0.22$). In the same way, we analyzed von Willebrand factor-positive signals at the lesion epicenter. Values were 23 ± 12.0, and 17.6 ± 5.2, for the bFGF – GH and GH groups, respectively. No statistically significant difference between groups was observed ($P = 0.83$).

The CGRP signals from the posterior funiculus on the rostral and caudal sides of the lesion epicenter were analyzed and compared. CGRP-positive fiber counts were 7.1 ± 2.6 and 35.2 ± 6.5 for the bFGF–GH and GH groups, respectively, and none of the differences were statistically significant ($P = 0.17$).

Discussion

Although we injected bFGF-incorporated GH 1 week after SCI in our experimental model, the optimal timing of bFGF injection remains an unresolved issue. Several studies, though, have provided suggestive data. For instance, one study detected significant increases in various molecular forms of FGF2 protein 4 days after SCI.[13] Another study showed significant up-regulation of bFGF 3 days after SCI, when cell proliferation is maximal.[14] A third study tracked bFGF mRNA, which initially was detected 1 hour post-injury, increased between 6 hours and 3 days, declined thereafter, and returned to baseline levels by 21 days.[15] These reports together indicate that up-regulation of bFGF is maximal 3 days after SCI and gradually decreases after that, from which we deduce that in terms of timing, it is best to wait until after bFGF up-regulation has peaked before injecting bFGF. Furthermore, another study showed that epidermal growth factor and FGF2 injection immediately after SCI had no impact on BBB scores for 8 weeks.[16] On the basis of all these studies, we decided to inject bFGF-incorporated GH 7 days after SCI.

We measured BBB scores for 9 weeks after SCI and also performed Rota-rod and inclined plane testing at several time points after SCI. The locomotor measurement data showed no statistically significant recovery in this study. bFGF – GH and GH-only injections appear to have had almost identical effects on injured spinal cords. In other words, both the bFGF – GH and the GH injections may have improved the ability of injured rats to perform weight-bearing activity. While the saline-injected SCI model rats that suffered the same contusion injury of the spinal cord did not reach weight-bearing levels in their BBB scores in our previous study,[1] rats of both groups in this study were able to perform weight-bearing activity. This result implies the possibility that GH itself has neuroprotective effects. Further investigation is needed to clarify this point. To examine associated histological changes, we assessed cortico-spinal tract tracing 2 weeks before sacrifice. Comparisons of BDA signals did not show statistically significant differences between groups. This histological finding supports the locomotor assessments in which bFGF

– GH and GH-only injections showed no statistically significant recovery in this study.

We measured two types of allodynia using a Hargreaves device and a dynamic plantar aesthesiometer. We observed no statistically significant differences between groups and in comparison with pre-injury rats, in mean thermal latency using the Hargreaves device. With respect to mechanical allodynia using the dynamic plantar aesthesiometer, while the GH injection group showed significantly more mechanical allodynia than the pre-injury data, the bFGF – GH group showed no statistically significant threshold changes compared with pre-injury. Although no statistically significant differences in the posterior funiculus CGRP-positive fiber counts between rostral and caudal sides of the lesion epicenter were observed, CGRP-positive fiber counts were lower in the bFGF – GH group. The histology data thus show some correspondence with the mechanical allodynia testing data, i.e. the bFGF – GH injection group had significantly less sensitivity to mechanical allodynia.

Conclusion

To summarize, the findings of this study revealed that the bFGF – GH group showed no statistically significant threshold changes compared with pre-injury, whereas the GH-alone group showed significantly more mechanical allodynia than the pre-injury data for that group. We had hoped to provide evidence that bFGF – GH could create a better environment for spinal cord regeneration. In the present study, although the bFGF – GH group showed almost identical amounts of recovery in comparison with GH group, we conclude that bFGF – GH created better conditions for decreasing sensory abnormalities.

Conclusion

Although we found few significant effects of bFGF – GH therapy, our results did provide evidence that bFGF-incorporated hydrogel treatment may possibly relieve mechanical allodynia following SCI and should be comparatively safe in future clinical use.

Acknowledgement

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LETTER TO THE EDITOR - SPINE

Drop finger caused by 8th cervical nerve root impairment: a report of six cases

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Dear Editor,

We would like to report the cases of drop finger caused by 8th cervical nerve root impairment (C8 drop finger).

Drop finger is a known manifestation of posterior interosseous nerve (PIN) palsy [1, 4]. Recently, C8 drop finger has been reported [3, 5, 6]. This symptom is difficult to distinguish from PIN palsy, possibly resulting in a delay of diagnosis [6]. Here, we report six cases of C8 drop finger to reveal its clinical features.

The present study included six cases (all in men, average age 57.2 years) diagnosed as C8 drop finger, of which muscle strength of extensor digitorum communis (EDC) showed a manual muscle testing (MMT) grade of 3 or less at our hospital. We retrospectively investigated clinical findings of those C8 drop finger patients.

In four patients, the symptoms were slowly progressive, whereas the remaining two patients experienced arm pain followed by acute finger drop. The initial diagnosis was PIN palsy. The duration from manifestation to diagnosis was 1–7 months (average 2.7 months). Muscular weakness was observed at EDC in all of the cases (MMT 2/5 or less), and in flexor digiti minimi (FDM), abductor digiti quinti (ADQ), and adductor pollicis brevis (APB). Atrophy in the first dorsal interosseus muscle was observed in four cases. There was no sensory disturbance except for in one patient. The electromyogram showed neurogenic discharge in EDC, FDM, ADQ and APB in all cases. Nerve conduction velocity analysis showed no apparent abnormalities. Magnetic resonance imaging (MRI) and computed tomographic myelogram (CT myelogram) revealed a C7-T1 foraminal stenosis on the affected side. Posterior laminoforaminotomy was performed in four cases. The muscle strength of EDC recovered at least 2 grades in MMT grade. The remaining two patients were treated with a neck collar because they refused surgery, although we recommended it. Weakness of finger extension in those conservatively treated patients did not show recovery.

A 67-year-old man showed acute drop finger. Initial diagnosis in the orthopedic clinic was PIN palsy. The patient's MMT of the right EDC was grade 1. He also showed weakness at his ADQ. There was a muscular atrophy at the first dorsal interosseous muscle. An electromyographic study revealed neurogenic changes in EDC, FDM, APB and ADQ. Preoperative MRI and a CT myelogram demonstrated stenosis of right C7-T1 intervertebral foramen (Fig. 1a and b). A laminoforaminotomy was performed at C7–Th1 level (Fig. 1c). Muscle strength of the right EDC recovered to 4/5 in MMT.

The PIN originates from C7 and C8 nerve roots and supply nerve fibers in extensor muscles [1]. Intrinsic hand muscles are innervated by ulnar and median nerves [2]. Therefore, PIN palsy never induces weakness of intrinsic hand muscles. By contrast, the C8 nerve root supplies its nerve fibers to the radial nerve and partially to ulnar nerve. Thus, impairment of the C8 nerve root can cause weakness of EDC and hand intrinsic muscles simultaneously [2]. Previous reports and the present

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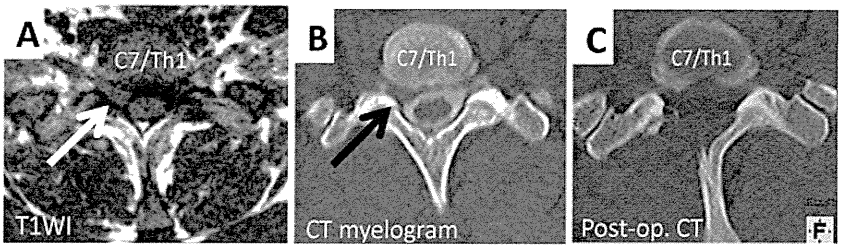

Fig. 1 Pre-operative and post-operative radiological findings of the representative case. Axial view T1-weighted MRI (**a**) and CT meylography (**b**) at C7/Th1 level revealed right sided foraminal stenpsis caused by disk herniation (*arrows*). After laminoforaminotomy, C7/Th1 intervertebral foramen was released (**c**)

cases show that C8 nerve root impairment alone is sufficient to cause drop finger [3, 5, 6]. We operate for C8 drop finger as soon as possible, since there is a possibility that a long-lasting severe weakness may lead to poor recovery. Tanaka et al. reported that half of their cases showed poor recovery after surgical treatment [6]. They speculated that the delay of diagnosis led to neuromuscular degeneration, resulting in poor surgical outcome. Early diagnosis might be important for a better surgical outcome. The present study reveals that C8 nerve root impairment alone can cause drop finger, and concomitant intrinsic hand weakness is key feature by which to distinguish C8 drop finger from PIN palsy.

Conflicts of interest None.

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