Introduction

With the progressive aging of society, increasing numbers of patients are presenting with cervical myelopathy and opportunity for diagnosis is increasing. In advanced cases, the symptoms and signs of cervical myelopathy consist of complaints of gait disturbance, clumsiness, and paresthesias of the hands with clinical signs of pyramidal tract and posterior column involvement. However, the clinical presentation can be atypical. For instance, patients may complain of paresthesias or clumsiness, without showing abnormal clinical neurological signs or it may be difficult to localize the lesion in patients who show pyramidal tract signs.

Severe myelopathy often shows poor prognosis even after surgical treatment. In diagnosis of myelopathy, severe spinal cord compression is often accompanied with mild symptoms, and mild compression with severe neurological symptoms, when spinal compression is evaluated by magnetic resonance imaging (MRI) or myelogram. If complication with other neurological disorder (spinal cord disorder other than of cervical spine, such as cauda equina disorder, diabetic peripheral neuropathy, or cerebral infarction, etc.) exists, it results in presentation of an atypical clinical symptom. In the case of patients with cervical sprain who present increased tendon reflexes and with myelopathy-like symptoms, surgical indication is difficult to determine. Electrodiagnosis, a functional diagnosis method, is feasible in such cases,[1,2)] and spinal cord evoked potential measurement is used routinely in Japan, however it is slightly

invasive. On the other hand, non-invasive and painless stimulation of deep nervous system including cerebral cortex and peripheral nerve could be achieved by transcranial magnetic stimulation, which would enable implementation of multiple tests pre- and post-operatively, and could provide objective evaluation of motor function which is necessary in ADL evaluation.[3,4,5)]

In this report, we will introduce the basics and cautions regarding the transcranial magnetic stimulation method and investigate its usefulness and problems in assessment of cervical myelopathy on the basis of our experience in using the method in severity assessment of myelopathy surgical indication determination and prediction of post-operative prognosis.

Materials and Methods

Subjects of this study included 56 patients (42 male and 14 female) who underwent surgery with diagnosis of cervical myelopathy and had central motor conduction time (CMCT) measured pre-operatively between June 1997 and April 2001 (3 year and 11 month period). Patients were aged 46 to 86 years (mean 64.5 ± 10.3) at the time of surgery, and the pre-operative clinical disability scores according to a modified ADL scale for cervical myelopathy of the Japanese Orthopaedic Association (JOA score: 0-17; 17 represents full function) (Table 1) were 5 to 15 points (mean 10.6 ± 2.8). The study group consisted of patients with cervical spondylotic myelopathy (39 patients), cervical posterior longitudinal ligament ossification (14 patients), cervical disc herniation (2 patients), and cervical yellow ligament calcification (1 patient), who were operated by French door laminoplasty (52 patients) or open door laminoplasty (4 patients). JOA score measurement (before and 1 year after surgery) and a 10-second grip and release test were performed for clinical disability assessment, and the Hirabayashi method was used for recovery rate evaluation.

For statistical analysis, Student's t-test and Spearman rank correlation test were performed using StatView (SAS Institute, Cary, NC), with significance of $p < 0.05$.

(1) Mechanism of transcranial magnetic stimulation

1. Principle

Faraday's principle of electromagnetic induction is applied for the method. An alternating magnetic field is generated by short-term discharges of current (time constant: < 0.3 ms) from a capacitor to a coil to induce eddy currents in the body tissue. These eddy currents flow in reverse direction to the current in the coil. From this property and information about the arrangement and direction of deep nervous system to be stimulated, optimal stimulation sites and directions can be determined.

In painless and noninvasive stimulation of the deep nerve system, magnetic stimulation has advantages compared to electric stimulation, because magnetic stimulation reaches deeper tissue with smaller attenuation.

2. Stimulation device

A MAGSTIM 200 monophasic transcranial stimulator (Magstim Co., Wales, U.K.) with a round coil (outside diameter, 110 mm) was used in this study.

3. Evoked potential recording system and electrodes

A general evoked potential recording system or electromyograph with 4 channels or more is preferable. Recording electrodes should be placed on left and right sides individually and on surfaces of upper and lower extremities (negative, belly muscle;

positive, tendon).

4. Testing positions of patients

Patients are tested while awake and sitting on a chair or bed. Paralysed patients are tested in the supine position on a bed.

(2) Stimulation and recording method and evaluation

After selecting the most adequate stimulation and recording methods, motor evoked potentials (MEP) should be evoked in extremity muscles by magnetic stimulation of the head, neck, and lower back. In the head stimulation, anterior horn cells in motor cortex are stimulated both directly and indirectly, and in the neck and lower back stimulation, the nerve root is stimulated at intervertebral foramen. From measured difference in latency time between head and neck, and head and lower back, (simple) CMCTs that represent latency time from brain to nerve root of neck and lower back are determined. F-waves and M-waves are then recorded and F-values are calculated to determine CMCT (F), which represents the conduction time from brain to spinal anterior horn. In this study, no response or a latency time of 1 SD or higher than that of the mean value in healthy volunteers was judged abnormal.

(3) Measurement method and caution

The coil (double core type) should be placed on the parietal region and stimulations 20 to 30% above threshold (maximum 100%) applied to the motor area at least two times, to ensure obtainment of reproducible MEP values. In the general procedure, records from 4 channels are obtained from both right and left sides at abductor pollicis brevis (APB), abductor digiti minimi (ADM), tibialis anterior (TA), and abductor hallucis (AH). To determine simple CMCT, stimulation is applied first to the head, followed by stimulation of cervical spine (C7 spinous process) and lumbar spine (middle point between L5 and S1 spinous process) to record latency times of APB, ADM, TA, and AH in the right and left sides of the body. Differences between left and right in these latency times represent simple CMCTs, which are conduction times from motor area to spinal nerve root. To determine CMCT (F), F-waves and M-waves are recorded by electric stimulation of median nerve (carpal region), ulnar nerve (carpal region), common peroneal nerve (fibra head), and tibial nerve (tarsal region), and F-values can be calculated from Kimura's formula[6] ((F+M-1)/2). The difference between F-value and latency time from head is then calculated to obtain CMCT (F), which is the conduction time from the motor area of the brain to the spinal anterior horn (Table 2). Following these procedures, approximate severity of motor pathway disorder and difference between right and left side can be estimated and conduction speed from spinal cord and cauda equina can also be obtained.

(4) Safety

Safety studies of this procedure have been conducted from multiple aspects and no adverse reaction has been reported in human or animal studies. The maximum current evoked by this magnetic stimulation system reported by Barker et al[5] was approx. 50 μc/pulse, which is only 1/2000 to 1/20000 of the current volume used in electroconvulsive therapy (100 mc to 1C), and the maximum current evoked was approx. 0.25A, smaller than the current evoked by the electric stimulation system of Merton et al[7]. Heat generation in tissue by this method is estimated at 2 mW or less, which is less than 1/300 of the international standard. The maximum magnetic field strength used is similar to that of static magnetic fields used in MRI, and the action time is very short. Various studies regarding relation to atrial fibrillation also concluded that there is no safety-related concern.[8]

As mentioned above, this method was demonstrated to be highly safe, but careful and strict selection of subjects is essential in clinical implementation. Patients with history of epilepsy, electrical implants such as cardiac pacemakers, or affixed magnetic bodies such as intracranial surgery clips should be ruled out. In cases such as cervical myelopathy with mechanical pressure in spinal canal, the patient should wear a neck collar to prepare for body movement.

Results

Right/left (normal control) pre-operative CMCT values for APB, ADM, TA, and AH were 12.3 ± 4.4 ms/12.1 ± 4.2 ms (9.4 ± 1.0 ms), 11.5 ± 4.0 ms/12.2 ± 3.1 ms (6.2 ± 1.4 ms), 18.3 ± 5.4 ms/17.8 ± 5.7 ms (14.3 ± 2.3 ms), and 18.5 ± 5.3 ms/18.9 ± 4.2 ms (14.9 ± 2.0 ms), respectively. These values showed prolongation compared to those of normal subjects reported by Kameyama[9] or Iizuka[10].

As for the relationship between the pre-operative JOA score and symptomatic side CMCT data, the pre-operative JOA score and CMCT (TA) showed slight correlation, while the pre-operative JOA score and CMCT (APB), CMCT (ADM), and CMCT (AH) were significantly related (Table 3). Comparing the upper or lower limb motor function score and symptomatic side CMCT data, the pre-operative upper limb motor function score showed significant correlation with CMCT (APB) and CMCT (ADM), while data for pre-operative lower limb motor function and CMCT (TA) and CMCT (AH) were also significantly related (Table 4). In a comparison of the 10-second grip and release test and upper limb CMCT data, significant relationship existed between the results from the grip and release test and CMCT (APB) and CMCT (ADM), though the correlation coefficients were small (Table 5). Between the symptomatic side CMCT data and one-year post-operative JOA score, the JOA score and CMCT (APB), CMCT (ADM), and CMCT (AH) showed significant correlation, i.e., subjects with prolonged

pre-operative CMCT showed lower one-year post-operative JOA scores (Table 6). As for the correlation between symptomatic side CMCT and upper and lower limb motor function score, subjects with prolonged CMCTs (except for CMCT (AH)) showed lower one-year post-operative upper and lower limb motor function scores (Table 7).

Evaluating the subjects by JOA score (Hirabayashi method), we classified subjects with recovery rates 60% or more as good outcome and 40% or less as poor outcome. Pre-operative CMCT (APB) values in good and poor outcome groups were 10.8 ± 3.6 ms (mean ± SD) and 13.7 ± 2.9 ms, respectively, and CMCT (ADM) values were 11.5 ± 3.5 ms and 14.9 ± 1.2 ms, respectively, showing significant prolongation in the poor outcome group (Fig. 1). In lower limb CMCT, CMCT (TA) levels in good and poor outcome groups were 16.7 ± 4.8 ms and 21.4 ± 5.3 ms, respectively and CMCT (AH) values were 18.3 ± 4.9 ms and 21.9 ± 3.5 ms, respectively, showing significant prolongation in the poor outcome group (Fig. 2).

A latency time of 1 SD or higher than that of the mean value in healthy volunteer[9)10)] was used for the evaluation of the CMCT prolongation. CMCT values for APB, ADM, TA, and AH on the symptomatic side showed prolongation in 42 cases (75%), 50 cases (89.3%), 42 cases (75%), and 37 cases (66.1%), respectively, among the 56 patients. Of the 56 patients, 28 (50%) showed increased CMCT in APB, ADM, TA, and AH. Of the 56 patients, 52 (94.6%) showed intramedullary high signal intensity in MRI while the 3 (5.4%) patients without intramedullary high signal intensity didn’t show increased CMCT in APB, ADM, TA, and AH on the symptomatic

side.

Discussion

Since the introduction of transcranial magnetic stimulation of the human motor cortex, the painless and noninvasive assessment of central motor conduction has become a useful diagnotic method. There are different reasons for delayed CMCT: slowed conduction in demyelinated corticospinal fibers, conduction along other oligosynaptic pathways, or reduction of size and synchrony of corticospinal volleys reaching the anterior horn cells[11].

In function tests of myelopathy, electrophysical methods including needle electromyogram and F- and W-wave measurements are routinely employed. However, these are indirect measurements and direct evaluation of spinal conduction function is not possible with them. Another spinal conduction test, the somatosensory evoked potential (SSEP), is mainly focused on sensory pathway and does not reflect motor pathway function. The recent development of transcranial magnetic stimulation has enabled evaluation of the motor nerve system's conduction pathway,[12] and this method is applied to objective evaluation of myelopathy.

In diagnosis of cervical myelopathy, conventional diagnostic methods such as neurological findings, MRI, and myelogram are usually performed, but conclusive diagnosis is sometimes difficult because many symptoms tend to be differentiated from the existing disease. In this regard, transcranial magnetic stimulation could be an effective diagnostic tool. Transcranial magnetic stimulation also has potential to enable

early diagnosis of myelopathy, by detecting changes in CMCT and in MEP wave forms that reflect conduction times of the pyramidal tract, because early pathological changes of cervical spondylotic myelopathy includes demyelinating of the pyramidal tract.[13,14] In accordance with the result of a study by Iizuka[15] and Kameyama et al.[9], which demonstrated significant prolongation of upper limb CMCT in subjects with cervical myelopathy compared to control and correlation with severity of symptom, this study showed correlation between upper/lower limb CMCT and JOA score, presenting the possibility of quantitative evaluation of the myelopathy by transcranial magnetic stimulation. Furthermore, this test method has advantages in the evaluation of patients who have developed severe joint deterioration due to rheumatoid arthritis or who have difficulty in communication and, therefore, for whom neurological detection is difficult.

In 1987, Ono et al.[14] reported specific hand deformity, loss of function, and marked lateral spine demyelination in pathology of cervical myelopathy, and defined myelopathy of hand by presentation of finger escape sign and slow grasp/release in a 10-second grip and release test. In this study, the results of 10-second tests correlated with upper limb CMCT and demonstrated the usefulness of these variables in quantitative evaluation of cervical myelopathy.

In a comparison between CMCT data and surgical outcome, Kameyama et al[16] reported poor prognosis in patients with prolonged pre-operative CMCT and with enhancement of intensity in spinal compressed region in T2 contrast MRI image, because of irreversible changes in spinal cord. Okada et al[17] also reported a significant

relationship between CMCT and post-operative JOA score or recovery rate determined by the Hirabayashi method, demonstrated by regression analysis of pre-operative variables in cervical myelopathy to detect the relationship. This report also showed significant prolongation in pre-operative upper and lower limb CMCT in poor prognosis patients compared to those with good prognosis, and pre-operative CMCT in upper and lower limb longer than 13 ms and 21 ms, respectively, predicted poor prognosis.

Transcranial magnetic stimulation showed potential in quantitative diagnosis as well as qualitative diagnosis in chronic compressive cervical myelopathy. This method is comparable to the magnetic stimulation system reported by Barker et al.[2)] This evaluation method is also useful in the process of informed consent by estimating post-operative recovery rate.

Conclusion

In patients with cervical myelopathy, the CMCT significantly correlated with the results of clinical assessment. These findings regarding the duration of CMCT may be useful parameters in spinal pathology for prediction of the outcome of surgical treatment.

Figure legends

Fig 1. Comparison of pre-operative upper limb CMCT between good and poor prognosis groups

Significant prolongation of CMCT (APB) and CMCT (ADM) were observed in poor prognosis group compared to good prognosis group.

Fig 2. Comparison of upper limb CMCT between good and poor prognosis group

Significant prolongation of CMCT (TA) and CMCT (AH) were observed in poor prognosis group compared to good prognosis groups.

Key Points

- The average CMCT of the symptomatic side significantly correlated with the pre-operative JOA score, i.e., patients with lower JOA scores had longer CMCTs.
- The average CMCT of APB and ADM muscles significantly correlated with the grip and release test results, and average CMCT of the symptomatic side with the one-year post-operative JOA score.
- The average CMCT for patients with poor outcome (recovery rate ≤ 40%, n=16) was significantly longer than that for patients with good outcome (recovery rate ≥ 60%, n=17).
- CMCT of 15 ms or more in the upper extremities or that of 22 ms or more in the lower extremities indicated poor prognosis.

Mini abstract

In patients with cervical myelopathy, the central motor conduction time (CMCT) significantly correlated with the results of clinical assessment. These findings regarding the duration of CMCT may be useful parameters in spinal pathology for prediction of the outcome of surgical treatment.

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Abstract

Study Design. This study investigated the clinical usefulness of motor evoked potentials (MEPs) produced by transcranial magnetic stimulation of the brain for cervical myelopathy patients.

Objectives. The purpose of this study was to determine the usefulness of MEPs for the assessment of the severity of myelopathy and prediction of the outcome of laminoplasty.

Summary of Background Data. Magnetic stimulation has been widely used for examination of the descending excitatory motor pathways in the central nervous system, but little attention has been paid to cervical myelopathy.

Methods. We measured the MEPs of 56 patients who underwent surgery for cervical myelopathy. The MEPs from the abductor pollicis brevis (APB), abductor digiti minimi (ADM), tibialis anterior (TA), and abductor hallucis (AH) muscle were evoked by transcranial magnetic brain stimulation. The latency from the anterior horn cell of the spinal cord to the hand or foot muscles was also measured, with the F-value [(F+M-1)/2] calculated. This was followed by estimation of the central motor conduction time (CMCT). Severity of clinical disability was scored on the basis of symptoms according to a modified ADL scale for cervical myelopathy of the Japanese Orthopaedic Association (JOA) score.

Rsults. The average CMCT of the symptomatic side significantly correlated with the pre-operative JOA score. The average CMCT of the symptomatic side significantly correlated with the one-year post-operative JOA score. The average CMCT for patients with poor outcome was significantly longer than that for patients with good outcome. CMCT of 15 ms or more in the upper extremities or that of 22 ms or more in the lower extremities indicated poor prognosis.

Conclusion. In patients with cervical myelopathy, the CMCT significantly correlated with the results of clinical assessment. These findings regarding the duration of CMCT may be useful parameters in spinal pathology for prediction of the outcome of surgical treatment.

〔**Key word:** transcranial magnetic stimulation, central motor conduction time, cervical myelopathy〕

Table 1. ADL scale for cervical spondylotic myelopathy (modified from the scale proposed by the Japanease Orthopaedic Association).*

Ⅰ. Motor dysfunction of upper extremity
- 0—Unable to feed oneself
- 1—Unable to handle knife and fork, able to eat with spoon.
- 2—Handle knife and fork with considerable difficulty
- 3—Handle knife and fork with slight difficulty
- 4—None

Ⅱ. Motor dysfunction of lower extremity
- 0—Unable to walk
- 1—Able to walk on a flat floor with walking aid
- 2—Able to walk up and/or down stair with handail
- 3—Lack of stability and smooth reciprocation, but able to walk unaided
- 4—No dysfunction

Ⅲ. Sensory deficit

A. Upper extremity
- 0—Severe sensory loss
- 1—Mild sensory loss
- 2—None

B. Lower extremity (same as A)

C. Trunk (same as A)

Ⅳ. Sphincter dysfunction
- 0—Unable to void
- 1—Marked difficulty in micturition
- 2—Difficulty in micturition
- 3—None

*Adapted from Yonenobu et al.[18]

Table 2: CMCT which was calculated from the formula[6)]

CMCT＝（latency time from head）－（F＋M－1/2）

Table 3:

Preoperative JOA score v.s. symptomatic side CMCT data

			correlation coefficient	p value
JOA score	v.s. CMCT	(APB)	-0.48	0.0006
	v.s.	(ADM)	-0.40	0.0051
	v.s.	(TA)	-0.34	0.0213
	v.s.	(AH)	-0.45	0.0025

Table 4:

Pre-operative the upper and lower limb motor function v.s. symptomatic side CMCT

		correlation coefficient	p value
Upper limb motor function score v.s. CMCT	(APB)	-0.58	<0.0001
v.s.	(ADM)	-0.43	0.0026
Lower limb motor function score v.s. CMCT	(TA)	-0.55	0.0001
v.s.	(AH)	-0.55	0.0001

Table 5:

Pre-operative 10-second grip and release test v.s. upper limb CMCT

		correlation coefficient	p value
10-second grip and release test v.s. CMCT	(APB)	-0.24	0.0247
v.s.	(ADM)	-0.23	0.0317

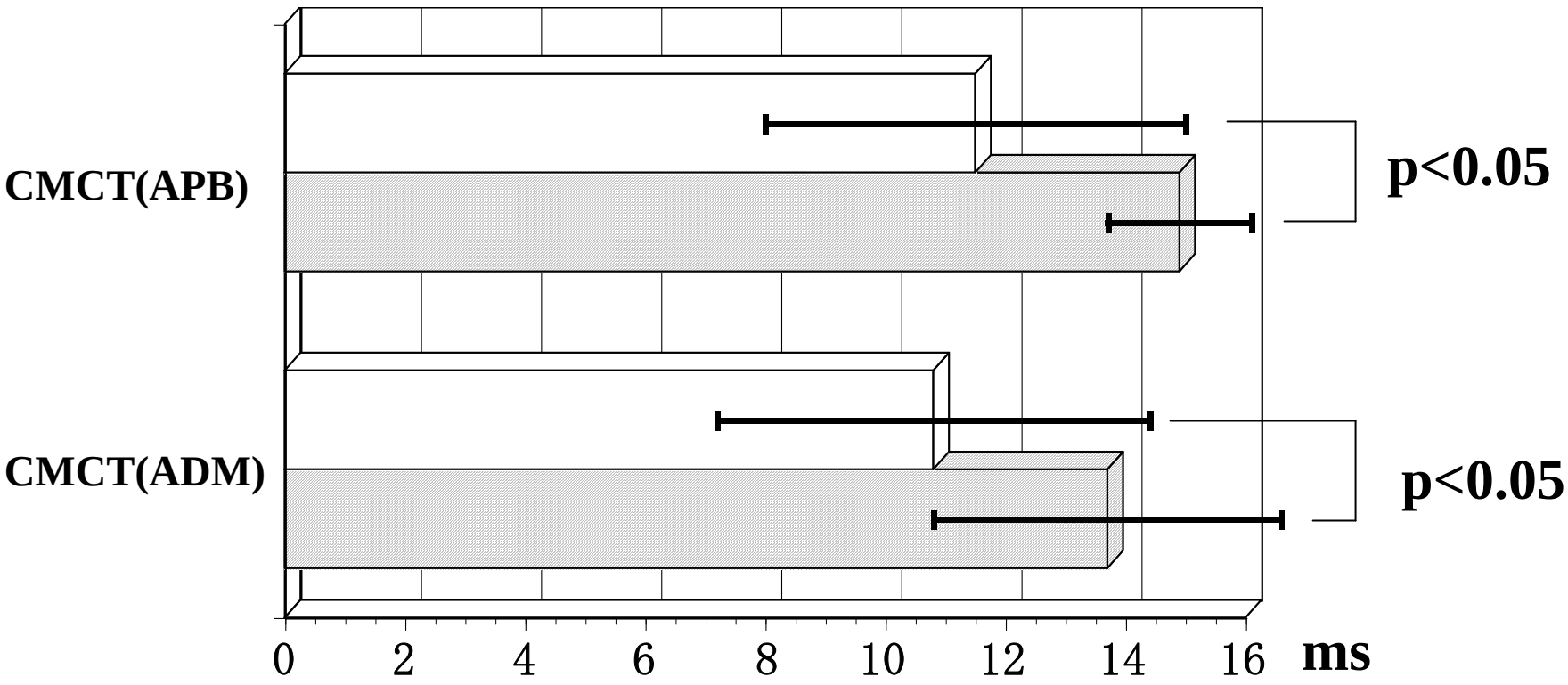
Table 6:
Symptomatic side CMCT data
v.s. one-year post-operative JOA score

	correlation coefficient	p value
CMCT(APB) v.s. JOA score	-0.40	0.0097
(ADM) v.s.	-0.42	0.0071
(TA) v.s.	-0.32	0.0405
(AH) v.s.	-0.40	0.0087

Table 7:

Symptomatic side CMCT data v.s. one-year post-operative upper and lower limb motor function score

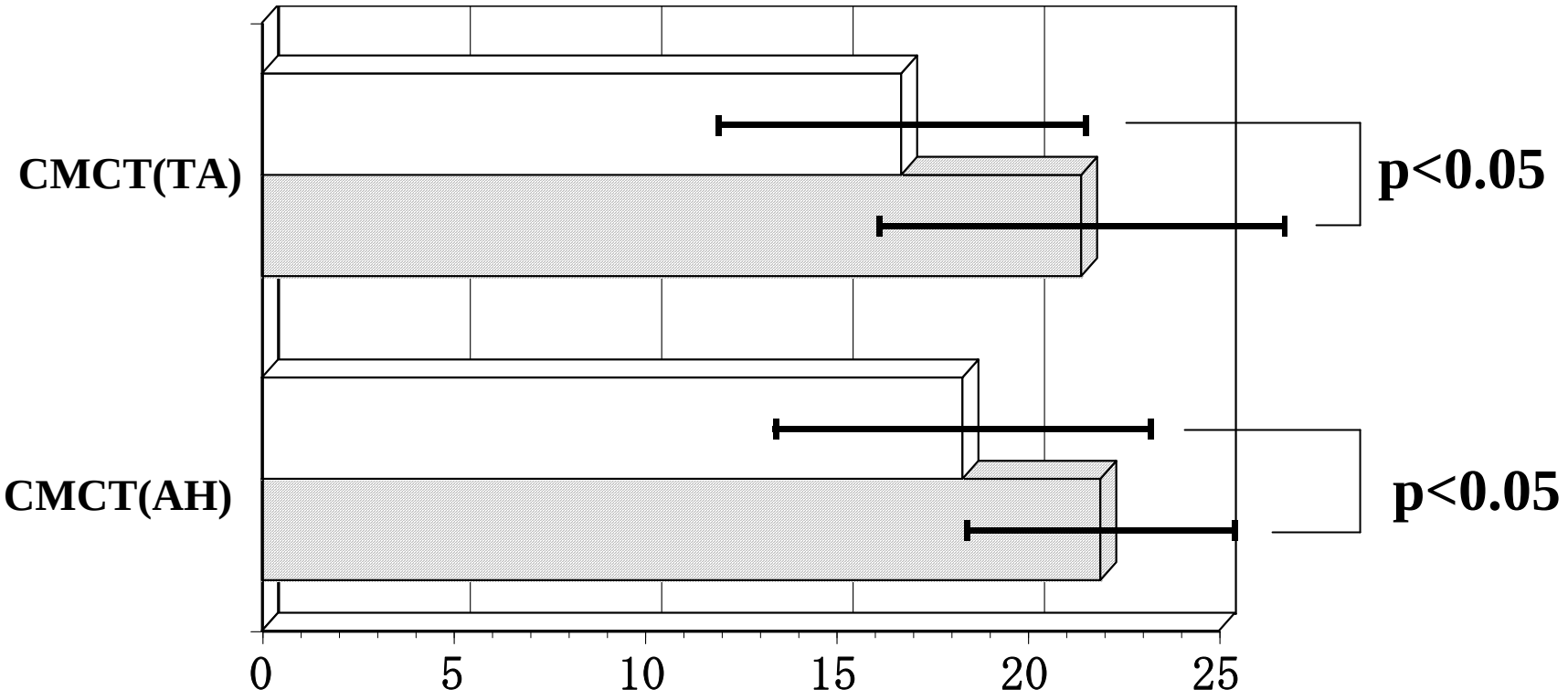
		correlation coefficient	p value
CMCT(APB)	v.s. upper limb motor function score	-0.34	0.0248
(ADM)	v.s.	-0.34	0.0273
(TA)	v.s. lower limb motor function score	-0.50	0.0015
(AH)	v.s.	-0.27	n.s.



Means±S.D.

Good outcome patients：Recovery rate ＞60%　n=17

Poor outcome patients　：Recovery rate ＜40%　n=16



Good outcome patients：Recovery rate ＞60%　n=17

Poor outcome patients　：Recovery rate ＜40%　n=16