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ORIGINAL REPORT

REORGANIZATION OF THE CORTICO-SPINAL PATHWAY IN PATIENTS WITH CHRONIC COMPLETE THORACIC SPINAL CORD INJURY: A STUDY OF MOTOR EVOKED POTENTIALS

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Objective: **To evaluate the change in motor evoked potential parameters following transcranial magnetic stimulation in patients with chronic complete thoracic cord injury.**
Design: **A cross-sectional study.**
Subjects: **Eighteen patients with chronic complete thoracic cord injury and 18 age- and sex-matched healthy controls were included in the study. The mean post-injury duration was 13.0 (standard deviation (SD) 6.0) years.**
Methods: **The latency, amplitude, central conduction time and peripheral conduction time of motor evoked potentials from bilateral abductor pollicis brevis and first dorsal interosseous muscles following transcranial magnetic stimulation were measured and compared between the patients and healthy controls. The predicting variables for central conduction time, including age, sex, height, illness duration and job activity, were analysed using a simple correlation and stepwise multiple regression model.**
Results: **The patients with complete thoracic cord injury had longer central conduction time recording of the dominant hand in both abductor pollicis brevis and first dorsal interosseous muscles. The difference in latency approached significance between the patients and controls. There was no statistical difference in amplitude between them. Regression analysis demonstrated that patients who were older, less physically active and with longer illness duration showed prolonged central conduction time.**
Conclusion: **The central conduction time in the dominant hand of chronic complete thoracic cord injury is prolonged. This study revealed motor reorganization of the central nervous system in complete thoracic cord injury. Decreased physical activity and prolonged illness may cause these changes.**

Key words: transcranial magnetic stimulation, motor evoked potential, spinal cord injury, reorganization, nerve conduction study.

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is a non-invasive technique for stimulating the motor cortex and is therefore suitable for neurophysiological studies in humans. TMS allows safe and painless assessment of the integrity of the descending motor pathway in the brain and spinal cord (1). Moreover, it can identify the cortical representation of a specific muscle with a time resolution of milliseconds, and has thus been widely and reliably employed in depicting short- and long-term reorganization of cortico-spinal motor output after spinal cord injury (2–8), hemispheric stroke (9, 10), limb amputation (11–13), transient anaesthesia (14) and rehabilitation training (15).

Spinal cord injury (SCI) incurs high mortality and morbidity. Due to the lack of an effective therapy, neurorehabilitation is still the conventional treatment for this debilitating ailment. Since the central nervous system is trainable, the design of more effective rehabilitation protocols, which take advantage of motor reorganization after SCI and do not just compensate for deficits, is an ongoing process in this field (16). Reorganization within the primary motor cortex was observed following SCI, but the pattern is variable. It is affected by many factors, including age of injury (17), location and extent of the lesion, and time since injury (18). The motor evoked potentials (MEP) following TMS of muscles caudal to the lesion after complete SCI are generally absent or increased in latency and threshold due to a block of the cortico-spinal pathway (5, 7, 8, 19). The cortical mapping of muscles rostral to the cord lesion is believed to expand after SCI. However, the change in the evoked potential latency following TMS is controversial, as there have been disparate reports showing no significant alteration (7), shortened central conduction latencies in injured patients (2, 20), and others showing the opposite results (6).

Plasticity of the undamaged cortico-spinal pathway is crucial to neurorehabilitation of those patients. We hypothesized that physical activity and age affect the reorganization process. The aim of this study was to examine the reorganization in patients with paraplegia with complete thoracic cord injury (CTCI) by evaluating the differences in the electrophysiological parameters of MEP elicited by TMS.

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MATERIAL AND METHODS

Subjects

Eighteen patients with CTCI (13 men, 5 women) and 18 sex- and age-matched healthy controls were recruited to this study following informed consent and institutional review board approval. The patients were recruited randomly from the member list of a local SCI Association with a mean age of 36.5 (standard devation (SD) 8.2) years and a mean height of 166.2 (SD 7.2) cm. Only patients who had had CTCI for more than one year were included in the study. Overall, the mean duration of CTCI was 13.0 (SD 6.0) years. Seventeen patients were victims of trauma. All patients belonged to the complete type (American Spinal Cord Injury Association Scale A) at the thoracic level. They were free from diabetes, uraemia, epilepsy, neurological deficits in bilateral upper extremities, a history of cranial surgery or skull fracture, and did not have a cardiac pacemaker. The score of job activity was defined as: 0 = no job (or less than 4 h/day), 1 = part-time job (or 4–8 h/day), 2 = full-time job (equal or more than 8 h/day). The healthy controls were matched for age (33.7 (SD 10.9) years), sex, and height (168.8 (SD 7.1) cm). All subjects' dominant side was on the right. The clinical details are shown in Table I.

Motor evoked potentials study by transcranial magnetic stimulation

Subjects were seated comfortably with their forearms supported on armrests. They were instructed to keep their arms relaxed with the hands and wrists in a neutral position. Magnetic stimulation was delivered with a Magstim 200 magnetic stimulator (Magstim Co., Whitland, Carmarthenshire, UK) through a figure-of-8 coil positioned tangentially to the scalp with the handle pointing backwards and the centre over the point of stimulation. The point of stimulation was 3 cm contra-lateral to the vertex on the interaural line (21). The intensity of magnetic stimulation was 100% of the maximum output of the device. MEPs elicited by TMS were recorded from bilateral abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles with surface electrodes in a belly-tendon montage according to the recommendations of the *ad hoc* International Federation of Clinical Neurophysiology Committee (21). The shortest latency, highest amplitude and largest area of consecutive 5 MEPs in each muscle were recorded with the connected electromyography system (Medelec Synergy, Oxford Instruments, UK), with the amplifier set at a bandpass filter of 16–3000 Hz.

Measurement of central conduction time

The median and ulnar nerves were stimulated by electrical stimulation applied at the level of the wrist. The intensity of stimulation was supramaximal. The skin temperature of the forearm ranged between 32°C and 35°C in all subjects. The shortest latencies of M and F waves were recorded. The central conduction time (CCT) was defined as the difference between the onset latency of MEPs to cortical stimulation and peripheral conduction time (PCT). The PCT is calculated from the latencies of M and F waves, as follows:

CCT = (latency of MEP) – (latency of M wave + latency of F wave – 1)/2 (22).

Statistical analysis

Data are presented as the mean and SD. Patients vs healthy controls and side-to-side comparisons of means were performed with the Mann-Whitney *U* test and the Wilcoxon signed-rank test, respectively. The univariate correlation analysis between CCT and predicting variables, including age, sex, height, cord injury, illness duration and job activity, was performed. The stepwise multiple regression analysis was then employed to eliminate the co-linearity between variables and to find a regression equation to predict CCT. The level of significance was set at $p < 0.05$ for all comparisons. Analyses were carried out using the SPSS 10.0® (Statistical Product and Service Solutions Inc., Chicago, IL, USA).

RESULTS

Compared with healthy controls, patients with CTCI had longer CCT in both the APB and the FDI muscles of the dominant hand. The patients with CTCI had longer MEP latencies obtained in the right APB muscles compared with healthy controls only approaching the level of statistical significance (Table II). Comparisons of bilateral values revealed longer PCT from both right APB and FDI muscles than left muscles in healthy controls (p-value = 0.031 for APB and 0.043 for FDI), with no side-to-side difference in patients with CTCI.

The simple correlation between CCT and variables, including sex, age, cord injury, height, illness duration and job activity, was performed first to determine the predicting factors. Age, cord injury and job activity correlated positively with CCT obtained in both APB and FDI muscles of the dominant hands, and the illness duration correlated with CCT obtained only in

Table I. *Neurological and clinical findings in the 18 patients with complete thoracic cord injury (CTCI)*

Case no.	Age (years)/sex	Cause of injury	Age at injury (years)	Level	Illness duration (years)	Current job	Job activity
1	40/M	Fall	18	T11	22	Taxi driver	2
2	40/M	Fall	24	T10	16	Taxi driver	2
3	24/F	Fall	7	T11	17	Student	1
4	37/M	TB spine	24	T4	13	Computer programmer	2
5	32/F	Traffic accident	20	T12	12	Telephone interviewer	1
6	39/F	Fall	27	T12	12	Lottery vendor	1
7	34/M	Traffic accident	17	T4	17	Assembler of pens	1
8	53/M	Traffic accident	30	T3	23	None	0
9	31/M	Traffic accident	25	T6	6	None	0
10	30/F	Fall	28	T11	2	None	0
11	26/M	Fall	25	T12	1	None	0
12	34/M	Traffic accident	19	T5	15	Computer programmer	2
13	28/F	Traffic accident	21	T11	7	Lottery vendor	1
14	45/M	Fall	29	T5	16	Lottery vendor	1
15	30/M	Traffic accident	15	T5	15	Computer programmer	2
16	46/M	Fall	35	T12	11	None	0
17	50/M	Traffic accident	37	T10	13	Lottery vendor	1
18	38/M	Traffic accident	22	T4	16	Computer programmer	2

M: male; F: female; T: thoracic; TB: tuberculosis.

Table II. *Comparison of transcranial magnetic stimulation parameters between healthy controls and patients with complete thoracic cord injury (CTCI)*

	Healthy controls		CTCI patients		*p*-value	
Parameters	R Mean (SD)	L Mean (SD)	R Mean (SD)	L Mean (SD)	R	L
APB muscles						
Latency (ms)	19.10 (1.30)	19.38 (1.90)	19.77 (0.88)	19.50 (1.16)	0.059	ns
PCT (ms)	14.21 (0.78)*	13.92 (0.72)*	14.13 (0.46)	14.02 (0.43)	ns	ns
CCT (ms)	4.89 (1.00)	5.47 (1.61)	5.63 (0.94)	5.48 (1.10)	0.007	ns
Amplitude (mV)	6.53 (1.73)	5.80 (2.00)	5.99 (2.40)	6.53 (2.27)	ns	ns
FDI muscles						
Latency (ms)	19.49 (1.50)	19.59 (1.34)	20.31 (1.48)	19.99 (1.24)	ns	ns
PCT (ms)	14.84 (1.00) †	14.49 (0.98) †	14.49 (1.00)	14.61 (0.94)	ns	ns
CCT (ms)	4.65 (1.04)	5.10 (0.92)	5.82 (1.10)	5.38 (1.34)	0.004	ns
Amplitude (mV)	6.97 (1.92)	5.73 (1.83)	5.17 (2.16)	5.53 (1.53)	0.020	ns

*$p = 0.031$ in bilateral comparison.
†$p = 0.043$ in bilateral comparison.
APB: abductor pollicis brevis; FDI: first dorsal interosseous; PCT: peripheral conduction time; CCT: central conduction time; ns: non-significant; R: right; L: left; SD: standard deviation.

FDI (Table III). In order to eliminate the effect of co-linearity, we used stepwise multiple regression analysis with CCT as the dependent variable, and sex, age, height, illness duration and job activity as the independent variables. The significant predictors of CCT were age and job activity in APB muscles of the dominant hand (Table IV). The regression equation of CCT in APB muscles of dominant hands = $3.998 + 0.056 \times$ age $-0.49 \times$ job activity. The predictors of CCT in FDI muscles of dominant hands were illness duration and age. The equation of CCT in FDI muscles of dominant hands = $3.351 + 0.042 \times$ age $+ 0.061 \times$ illness duration.

Table IV. *Partial correlation by utilizing stepwise multiple regression analysis*

	CCT of right APB			CCT of right FDI		
Independent variables	Partial correlation coefficient	R^2	*p*-value	Partial correlation coefficient	R^2	*p*-value
Sex	0.082	–	0.643	0.189	–	0.285
Age	0.546	0.242	0.001*	0.370	0.110	0.029*
Height	–0.238	–	0.175	0.109	–	0.538
Illness duration	0.081	–	0.649	0.420	0.193	0.012*
Job activity	–0.399	0.121	0.018*	–0.169	–	0.340

*Entered variable.
CCT: central conduction time; APB: abductor pollicis brevis; FDI: first dorsal interosseous.

DISCUSSION

The results of this study illustrate that CCT is prolonged in the MEP by TMS in both APB and FDI muscles, as recorded in the dominant hand of patients with chronic CTCI. This lengthened CCT significantly correlated with age and job activity. The CCT predominantly reflects the maximum speed of the activated fibres and a prolonged CCT may suggest an impaired temporospatial summation of cortico-spinal pathway or changes in cortical excitability. Hence, a significant central reorganization of the motor system had probably occurred in chronic CTCI patients. Our results are in accordance with an earlier report, which revealed increased latencies and decreased thresholds on the MEPs rostral to the cord lesion in patients with CTCI (6). Longer latencies in MEP rostral to cord lesion might be due to several factors, including a longer cortico-spinal activation process (6), less efficient synaptic function or changes in the pattern of synaptic connections due to de-afferentation (1). Deafferentation results in rapid reorganization of the sensorimotor area targeting the territories proximal to the disconnected region (18). Conversely, enhanced sensory feedback of a body part may increase the representation in the primary motor cortex of that body part (23). However, the mechanisms underlying this injury-induced plasticity cannot be elucidated in our study (24).

Table III. *Simple correlation of prediction factors of central conduction time (CCT)*

	CCT by right APB recording		CCT by right FDI recording	
Independent variables	Correlation coefficient	*p*-value	Correlation coefficient	*p*-value
Sex	0.249	0.143	0.294	0.082
Age	0.492	0.002*	0.392	0.018*
Cord injury	0.368	0.027*	0.491	0.002*
Height	–0.131	0.447	0.058	0.739
Illness duration	0.228	0.181	0.439	0.007*
Job activity	0.350	0.036*	0.528	0.001*

*$p < 0.05$.
APB: abductor pollicis brevis; FDI: first dorsal interosseous.

We used multiple regression analysis to determine the correlating factors of prolonged CCT. This method eliminates the effect of co-linearity and confounding. The results revealed that the change in CCT is significantly correlated with age and physical activity in APB muscles of the dominant hand, and is significantly correlated with age and duration of illness in FDI muscles of the dominant hand. No such correlation was observed in the non-dominant hand. It is not surprising that CCT, which reflects the conduction speed of the fastest fibres in the cortico-spinal pathway, is correlated with age. According to our regression equation, there is approximately 8% prolongation of the CCT per decade of age. This value is higher than the 3% increase per decade observed in the peripheral conduction studies (25). Some factors, other than increased demyelination or decreased synaptic efficiency due to ageing, may also affect the conduction speed in the cortico-spinal tract.

A previous report by Sanes & Donoghue (23) showed that an increase in motor activity could cause central reorganization with increased cortical representation of specific muscle and increased excitability. Since fast conducting fibres, which are usually larger in diameter, could mediate relative powerful movement, the central conduction time is correlated to physical activity. A study by Samii et al. (26) showed prominent evidence in patients with chronic fatigue syndrome who had a reduction in daily activities to less than 50% of the pre-morbid level for at least 6 months. These patients showed significant lower post-exercise MEP facilitation. Another classic study on proficient Braille readers revealed a significantly larger representation area of the FDI muscle (27). On the other hand, patients with an immobilized ankle joint for a mean duration of 16 weeks had reduced motor cortex area of the inactivated tibialis anterior muscle. The reduced area correlated with the duration of immobilization. These changes could be reversed by voluntary ankle movement (28). Thus, the parameters of MEP by TMS may be affected by both physical activity and inactivity. The daily physical activity is generally decreased and largely from the upper extremity in CTCI patients. All of the patients used self-propelled manual wheelchairs. The difference in the level of physical activity came largely from their employment. This is why employment activity was chosen as a surrogate of physical activity.

The time frame is also another key factor to organization. The central nervous system changes after injury can be induced not only in the short-term but also in the long-term (18). Rapid organization, occurring within minutes, can be observed after transient deafferentation (29). Motor reorganization following stroke can also occur after years of onset (30). It is reasonable to assume that duration of a condition contributes to the extent of reorganization. However, our analysis does not determine why only FDI was affected by illness duration.

In the present study, healthy controls had longer PCT in the MEPs from APB and FDI muscles in the dominant hands. The PCT, a parameter deduced from M and F wave latencies, revealed the conduction time of the fastest fibres between the alpha motor neuron and innervated muscle fibre. In a study of healthy individuals, longer latency, smaller amplitude, and slower distal conduction velocity of the sensory nerve were observed in right median and ulnar nerves (31). A similar result was obtained from another study on asymptomatic workers (32). This prolongation of conduction time might result from accumulation of multiple microtraumas to axons during physical activity. However, further study on the correlation of physical activity and the changes in PCT is needed in order to elucidate this mechanism.

A relatively small sample size for multiple regression analysis in the present study may decrease the power of test. However, the limited number of cases in this study was sufficient to achieve positive results. In the future, we will recruit bed-ridden patients who perform less physical activity than the healthy population, in order to verify a prolonged CCT and latency. Furthermore, the parameters of cortical excitability should be included in future studies in order to determine whether reorganization occurs at the level of the brain or the spinal cord (33).

In conclusion, this study verified the prolonged CCT of MEP by TMS in the APB and FDI muscles of dominant hands in patients with chronic CTCI. The prolongation was significantly related to older age, less physical activity and increased duration of CTCI. It further implied that decreased physical activity could result in reorganization in patients with chronic CTCI.

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