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PROGNOSTIC VALUE OF ELECTROPHYSIOLOGICAL PARAMETERS FOR THE RECOVERY OF MOTOR FUNCTIONS IN STROKE PATIENTS

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We estimated correlations between baseline electrophysiological parameters and motor functions in patients with subacute stroke, in order to identify their predictive value for motor and functional recovery after a 4-week-long rehabilitation period. Sixty patients with subacute stroke were enrolled. Somatosensory evoked potentials (SSEPs), compound motor action potentials (CMAPs), and sensory nerve action potentials (SNAPs) were recorded, and the amplitude ratios were calculated in the components of these potentials. Clinical parameters consisted of the Korean-modified Barthel index (K-MBI), motricity index (MI), and manual function test (MFT). After the rehabilitation period, these indices were re-evaluated. The ulnar CMAP amplitude was found to significantly correlate with all clinical outcome indices. Additionally, a multivariate linear regression analysis revealed that the ulnar CAMP amplitude ratio was an independent predictor for the baseline MI of the upper extremity and K-MBI. The median SSEP amplitude ratio was an independent prognostic factor for the follow-up MI of the upper extremity, MFT, and follow-up K-MBI. Our results indicate that *not only* is the median SSEP amplitude ratio a prognostic factor for the motor functions and functional recovery, *but also* the ulnar CMAP amplitude might be an independent predictor in subacute stroke patients.

Keywords*:* stroke, electroneurography, electromyography, somatosensory evoked potentials, prognostic value, motor recovery, functional recovery.

INTRODUCTION

Stroke is one of the major causes of disability that impairs the motor functions and activities of daily living (ADL) [1]. The optimal goal of comprehensive rehabilitation is to improve the basic mobility and ADL skills up to the maximal possible level. In addition, it is very important to predict the course of recovery, which is essential for setting the appropriate mode of rehabilitation therapy. Of many assessment tools, previous studies have reported that the parameters of somatosensory evoked potentials (SSEPs) could predict most adequately the functional outcomes of stroke [2-4].

To date, however, only few studies have discussed the predictive value of peripheral nerve conduction parameters. Within an early stage of the onset of stroke, there is a motor unit loss in patients with stroke on the hemiparetic side because of transsynaptic degeneration. In addition, it has also been suggested that there is a correlation between the motor unit loss and hemiparetic severity [5, 6]. We have, therefore, hypothesized that the peripheral nerve conduction parameters and those of SSEPs have a significant prognostic value.

The aims of this study were as follows:

(i) To analyze correlations between baseline electrophysiological parameters (e.g., the peripheral nerve conduction ones and those of SSEPs) and baseline motor and functional parameters in patients with subacute stroke.

(ii) To identify electrophysiological parameters with the highest predictive value for the motor and functional recovery after a 4-week rehabilitation.

METHODS

Subjects. In patients who were admitted to our hospital, stroke-related lesions involved unilaterally the cortical or subcortical areas, as confirmed by computed tomography (CT) or magnetic resonance

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imaging (MRI). Sixty subjects (26 men and 34 women) with a mean age of 66.5 years (range 38-89 years) had an onset of subacute stroke within three months. In our series, there were 46 cases of cerebral infarction and 14 cases of cerebral hemorrhage. Among the patients, there were 27 right-sided and 33 left-sided cases.

Inclusion criteria for our study are as follows: (i) relatively preserved level of consciousness; (ii) first cerebrovascular episode, and (iii) unilateral hemispheric lesion.

Among the exclusion criteria, there were: (i) cognitive loss or dementia; (ii) the presence of pacemaker or other electromedical implant devices; (iii) diabetes or peripheral neuropathy; (iv) convulsions; (v) neglect or visuospatial disorders; (vi) joint contractures and/or deformities, and (vii) intracranial metal implants.

Assessment of Electrophysiological Findings. Nerve conduction studies were performed by the use of "Medelec Synergy" EMG set (Medelec Synergy, Great Britain), for which the conventional techniques of percutaneous stimulation and surface electrode recording were used at a skin temperature of > 32°C. The condition of the motor nerves was evaluated by bilateral recording from the median nerves innervating the *mm. abductor pollicis brevis*, ulnar nerves innervating the *mm. abductor digiti minimi*, peroneal nerves innervating the *mm. extensor digitorum brevis*, and tibial nerves innervating the *mm. abductor hallucis*. The distance between the distal stimulation point and the active recording electrode was set at 70 mm in the upper extremities and 80 mm in the lower ones. This was followed by measurements of the latency, amplitude, and side-to-side (affected/sound side) amplitude ratio based on the compound muscle action potentials (CMAPs).

Sensory nerve conduction studies were performed bilaterally on the median, ulnar, superficial peroneal, and sural nerves with the placement of an active electrode at a 140 mm above position, for which the antidromic stimulation technique was used. At least 10 responses were recorded and then averaged. Standard low- and high- frequency filter settings were 20 and 10 kHz for the motor nerve conduction study and 20 Hz and 2 kHz for the sensory nerve conduction study. The latency, amplitude, and side-to-side (affected/sound side) amplitude ratio were measured based on the sensory nerve action potentials (SNAPs).

For SSEP investigation, the median nerve was stimulated at the wrist level with a frequency of 3 sec^{-1}, pulse duration 0.1 msec, and current strength enough to produce minimal twitches of the thenar muscle. Two traces of at least 250 averaged responses were recorded. Responses were recorded using scalp needle electrodes with the active one over contralateral C3/C4, while the reference was located at Fz. The posterior tibial nerve was stimulated at the ankle level; SSEPs were recorded from the Cz site with the reference electrode placed at Fz. The following parameters were measured bilaterally: N20 latency, N20-P25 peak-to-peak amplitude, and N20-P25 affected/sound side amplitude ratio during the median SSEP test. For the posterior tibial SSEP, the P40 latency, P40-N50 amplitude, and P40-N50 amplitude ratio were estimated. Among these data, we accepted the amplitude ratio of N20-P25, that of P40-N50, and CMAP, and SNAP parameters as the main electrophysiological indices.

Assessment of the ADL Function. The Korean-modified Barthel index (K-MBI) was used for characterization of the ADL functions. The MBI is a reliable and valid tool for measuring the functional status of the patients with stroke, and the Korean version of the MBI has been validated [7].

Assessment of the Motor Function. The motricity index (MI) was used to assess the motor impairment after stroke. The muscle strength for the upper and lower limbs was calculated as the MI for the following movements, shoulder abduction, elbow flexion, and wrist extension for the upper limb and hip flexion, knee extension, and ankle extension for the lower limb. Of several possible MI scores, we measured the hemiparetic side score, namely (side arm score + side leg score)/2 [8].

The manual function test (MFT) was used to assess the motor function of the upper extremities; it included eight subtests, namely forward elevation of the arm, lateral elevation of the arm, touching the occiput with the palm, touching the back with the palm, grasping, pinching, and carrying out cubes and pegboard manipulations. The ratings could vary from 0 (maximally severely impaired) to 32 points (full function).

All the assessments were performed at baseline evaluation and repeated four weeks after conventional rehabilitation therapies consisting of physical and occupational therapies focused on the mobility and ADL training.

Statistical Analysis. All statistical analyses were performed using the SPSS statistical package (version 12.0, SPSS Inc., USA). The Student's *t*-test was used to compare baseline values, such as the motor function, ADL function, and electrophysiological parameters according to the sex, stroke type, and lesion side. Pearson's correlation analysis was used to assess the relationships among baseline values of the motor function, ADL function, and electrophysiological parameters and to assess the relationships among electrophysiological parameters, follow-up motor function, and follow-up ADL function. Multivariate linear regression analysis using a backward selection linear regression model was employed to determine whether the baseline electrophysiological parameters were significant predictors of the motor and ADL functions at baseline and at four weeks after rehabilitation. *P* values below 0.05 were considered indications of statistical significance in intergroup comparisons.

RESULTS

Baseline Evaluation of the Electrophysiological Parameters. Mean values of these parameters, including the SSEP, CMAP, and SNAP amplitude ratios, are shown in Table 1.

Correlations among the ADL Function, Motor Functions at Baseline and Follow-Up, and Electrophysiological Parameters at Baseline. Correlations of nerve conduction parameters at baseline and clini-

T a b l e 1. Mean Values of the Amplitude Electrophysiological Parameters

Т а б л и ц я 1. Середні значення амплітудних електрофізіологічних параметрів

	Side-to-side amplitude ratio (%)
Median SSEP	0.48 ± 0.51
Tibial SSEP	0.59 ± 0.49
Median motor	0.84 ± 0.23
Ulnar motor	0.80 ± 0.22
Peroneal motor	0.85 ± 0.37
Tibial motor	1.01 ± 0.26
Median sensory	0.91 ± 0.41
Ulnar sensory	0.97 ± 0.35
Superficial peroneal sensory	0.66 ± 0.53
Sural sensory	0.97 ± 0.59

Footnotes: means ± s.d. are shown; SSEP, somatosensory evoked potential

T a b l e 2. Correlations among the ADL Function, Motor Functions at Baseline and Follow-Up, and Nerve Conduction Parameters at Baseline

Т а б л и ц я 2. Кореляції між функцією повсякденного життя (ADL), моторною функцією у вихідному стані і після реабілітації та параметрами нервового проведення у вихідному стані

Clinical parameter		Pearson's correlation coefficient (*r*)							
		MMAR	UMAR	PMAR	TMAR	MSAR	USAR	PSAR	SSAR
MFT	Baseline	0.24	0.52**	–0.16	0.25	0.19	0.27	–0.04	–0.11
	F-up	0.35	0.46**	–0.20	0.17	0.23	0.35	–0.04	–0.26
MI upper limb	Baseline	0.28	0.55**	–0.18	0.20	0.13	0.26	–0.10	–0.12
	F-up	0.21	0.38**	–0.13	0.15	0.15	0.19	–0.10	–0.03
MI lower limb	Baseline	0.08	0.44**	0.03	0.13	0.00	0.23	0.43	–0.11
	F-up	0.11	0.33*	0.07	0.19	0.06	0.19	0.10	–0.06
K-MBI	Baseline	0.15	0.34**	0.04	0.15	0.26	0.18	0.18	–0.05
	F-up	0.15	0.29**	0.08	0.20	0.25	0.23	0.24	–0.41*

Footnotes: MFT, manual function test; MI, motricity index; K-MBI, Korean-modified Barthel index; F-up, follow-up; MMAR, median motor amplitude ratio; UMAR, ulnar motor amplitude ratio; PMAR, peroneal motor amplitude ratio; TMAR, tibial motor amplitude ratio; MSAR, median sensory amplitude ratio; USAR, ulnar sensory amplitude ratio, PSAR, superficial peroneal sensory amplitude ratio, and SSAR, sural sensory amplitude ratio. * $P< 0.05$; ** $P < 0.01$.

T a b l e 3. Correlations among the ADL function, Motor Function at Baseline and Follow-Up, and SSEP Parameters at Baseline

Т а б л и ц я 3. Кореляції між функцією повсякденного життя, моторною функцією у вихідному стані і після реабілітації та параметрами соматосенсорних викликаних потенціалів у вихідному стані

Clinical parameter		Pearson's correlation coefficient (*r*)	
		Median SSEP amplitude ratio	Tibial SSEP amplitude ratio
MFT	Baseline	0.26	0.24
	F-up	0.35*	0.14
MI, upper limb	Baseline	0.23	0.19
	F-up	0.37**	0.24
MI , lower limb	Baseline	0.19	0.39**
	F-up	0.29*	0.38**
K-MBI	Baseline	0.08	0.21
	F-up	0.28*	0.27*

Footnotes: SSEP, somatosensory evoked potential; other designations are similar to those in Table 2.

cal measures of outcome consisting of the ADL and motor function before and after rehabilitation are summarized in Table 2. The side-to-side amplitude ratio of the ulnar CMAP demonstrated significant correlation with all clinical outcome indices, both at baseline and follow-up (Table 2). In multivariate linear regression analysis, the ulnar CMAP amplitude ratio among nerve conduction parameters was a significant independent factor of the baseline MI of the upper extremity (beta = 0.474, $P < 0.01$, adjusted $R^2 = 0.306$) and the baseline K-MBI (beta = 0.356, $P = 0.028$, adjusted $R^2 = 0.103$).

Correlations among the ADL function, motor functions at baseline and follow-up, and SSEP parameters at baseline are summarized in Table 3. The median SSEP amplitude ratio revealed significant correlations with the follow-up MI of upper extremity (r = 0.37, $P < 0.01$), follow-up MI of the lower extremity (r = 0.29, $P < 0.05$), and follow-up K-MBI (r = 0.28, P < 0.05). The tibial SSEP amplitude ratio revealed significant correlations with the baseline MI of the lower extremity (r = 0.39, $P < 0.01$), follow-up MI of the lower extremity (r = 0.38, $P < 0.01$), and follow-up K-MBI (r = 0.27, $P < 0.05$) (Table 3). According to multivariate regression analysis, the baseline MI of the upper extremity (beta = 0.848, $P < 0.001$) and median SSEP amplitude ratio (beta = 0.140, $P = 0.048$) were independent prognostic factors for the follow-up MI of the upper extremity (adjusted $R^2 = 0.792$). The baseline MFT (beta = 0.897, $P < 0.001$) and median SSEP amplitude ratio (beta = 0.176, $P = 0.024$) were independent prognostic factors for the follow-up MFT (adjusted $R^2 = 0.859$). The baseline K-MBI (beta = 0.424, $P = 0.010$), MI of the lower extremity (beta = 0.430, $p = 0.010$), and median SSEP amplitude ratio (beta = 0.251, $P = 0.010$) were independent prognostic factors of the follow-up K-MBI (adjusted $R^2 = 0.707$).

DISCUSSION

Our study demonstrated that the peripheral nerve conduction parameters and those of SSEP correlated with the motor and ADL functions in patients with subacute stroke. In addition, our results also showed that the ulnar CMAP amplitude ratio demonstrated strong correlation with the motor function of the upper extremity and ADL functions. Moreover, our results also showed that the median SSEP, as well as clinical parameters, can be considered independent prognostic factors for the motor function of the upper extremity, manual function, and ADL functions after a 4-week-long rehabilitation with the corresponding procedures.

To date, it is obvious that there are pathological modifications in motor units in patients with stroke lesions. Several studies suggested that there is a correlation between changes in the motor units on the hemiparetic side and severity of hemiparesis in patients with stroke [5, 6, 9-12]. In addition, some authors also believed that the decreased CMAP amplitude on the hemiparetic side might be indicative of the decreased number of motor units [9, 11]. Other authors, however, suggested that this may result from the loss of functioning motor units on the hemiparetic side in patients with stroke [10, 12].

Changes in the peripheral nerve function on the paretic side could be explained by various theories. Some studies demonstrated that alterations in the homeostasis and neurovascular regulation induced by changes in the tissue composition and fiber type distribution could occur on the paretic side in stroke patients [13, 14]. It has also been proposed that a decreased number of motor units on the hemiparetic side is due to transsynaptic degeneration of motoneurons caused by upper motor lesions [5]. Moreover, the decreased number of motor units would result from deprivation of trophic inputs received via descending motor pathways [15]. Kondo et al. [16] reported that, probably, there is a possible correlation between the extent of degeneration of the lateral corticospinal tract and fiber loss in the ventral roots of patients with stroke. Moreover, these authors also presumed that a transsynaptic effect of the degenerated lateral corticospinal tract promoted fiber loss in the ventral roots.

On the other hand, there is also a possibility that the lower motor injury might be involved after the onset of stroke. Van Kuijk et al. [17] have hypothesized that the lower motor neuron lesion manifested in axonal involvement might arise from an independent “dying back” neuropathy due to de-afferentation of lower motor units in patients with upper motor lesions. Based on this theoretical background, transsynaptic degeneration secondary to the upper motor lesion would be followed by further loss of motor units in patients with severe hemiparesis [5]. This suggests that the prevalent occurrence of degeneration was associated with a greater severity of hemiparesis.

Objective assessment of the current state and early prediction of the expected recovery can provide appropriate guidelines for rehabilitation therapy [18, 19]. Several studies were conducted to examine the relationship between various electrophysiological parameters and stroke outcomes. Hara et al. [5] examined the median motor F-wave, thus reporting that the number of motor units on the hemiparetic side was significantly smaller, as compared with the unaffected side, in patients with ischemic stroke who had a more than 9-year history of hemiparesis. These authors also noted that the degree of motor unit loss was significantly higher in patients with severe hemiparesis. It has also been reported that the persistent presence of the F-wave, obtained through repetitive stimulation of the ulnar nerve, is associated with the level of consciousness in patients with acute stroke [20, 21]. According to Lukacs [6], there was significant correlation between the ulnar CMAP amplitude, rather than ulnar SNAP and the severity of hemiparesis, in 48 patients with ischemic stroke. This finding agrees with our results. In the current study, however, we performed nerve conduction studies for various nerves, including the ulnar nerve in patients with stroke presenting with hemorrhage and ischemia. Moreover, we also evaluated the ADL functions, as well as the motor function, in these patients. Our results showed that the ulnar CMAP amplitude ratio demonstrated significant correlation with all considered baseline clinical indices in patients with subacute stroke. The multivariate linear analysis showed that the ulnar CMAP amplitude ratio can be interpreted as a significant predictor for the baseline MI of the upper extremity and the baseline ADL function. The parameters of the upper-extremity motor events at the subacute stroke phase had a higher clinical value than the parameters of the lower extremities for evaluation of progression of Wallerian degeneration after the stroke onset. It was considered that the prolonged time period elapsed until the appearance of electrophysiological abnormalities in the distal limb muscles was due to the greater segment of nerve degeneration [22].

Paolni et al. [23] reported abnormal findings of peripheral nerve conduction parameters on the sound side in patients with ischemic stroke, as compared with the normal controls. These authors also suggested that stroke is a primary cardiovascular event and that it might show a strong correlation with peripheral nervous system (PNS) disorders. Considering this, we selected the CMAP amplitude ratio as a sensitive parameter in screening minimal changes in the peripheral nerve conduction after the onset of stroke. Thus, we found that the ulnar CMAP amplitude ratio was a useful indicator for the post-stroke severity of the motor and ADL functions.

In addition, SSEPs are also an objective tool for assessing the integrity of sensory and motor pathways and the involved areas of the CNS.The alterations in SSEPs are significant prognostic indicators for the degree of proprioceptive loss [24]. Previous studies have reported that there is correlation between the SSEP parameters and clinical outcomes [2-4, 25, 26]. In our study, however, we evaluated the predictive value of the SSEP amplitude ratio with motor parameters at baseline [3, 4] rather than with central conduction delay, which has been widely accepted as a prognostic factor. We also found that there are strong correlations between the median SSEP amplitude ratio, follow-up MI of the upper limb, MFT, and K-MBI.

There are two limitations in our study: (i) we enrolled a relatively large number of patients in our study, but this number was not sufficient for the subgroup analysis, and (ii) a 4-week course of therapeutic intervention might be insufficient to achieve a complete recovery after the onset of stroke in some patients.

Further larger-scale and longer-term follow-up studies are, therefore, warranted to establish the prognostic value of certain electrophysiologic parameters.

In conclusion, our results indicated that *not only* is the ulnar CMAP amplitude an independent predictor of the upper-extremity motor and ADL functions in patients with subacute stroke, *but also* the median SSEP amplitude ratio might be a relatively strong prognostic factor for the motor functions of the upper extremity and functional recovery.

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All testing procedures were in accordance with the ethical standards of the responsible Committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Written informed consent was obtained from all patients for being included in the study.

The authors of this study, S. M. Kim, J. H. Kim, B. R. Kim, Ch. W. Hyun, and E. Yo. Han, declare that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations between co-authors of the article.

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ПРОГНОСТИЧНА ЦІННІСТЬ ЕЛЕКТРОФІЗІОЛОГІЧНИХ ПАРАМЕТРІВ ЩОДО ВІДНОВЛЕННЯ МОТОРНИХ ФУНКЦІЙ У ПАЦІЄНТІВ З ІНСУЛЬТОМ

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Р е з ю м е

Ми оцінювали кореляції між вихідними електрофізіологічними параметрами та моторними функціями у пацієнтів із підгострим інсультом з ціллю ідентифікувати прогностичну цінність цих даних для моторного та функціонального відновлення після чотиритижневого періоду реабілітації. Відводили соматосенсорні викликані потенціали (SSEP), складні моторні потенціали дії (CMAP) та складні сенсорні нервові потенціали дії (SNAP); розраховували відношення амплітуд цих потенціалів та їх компонентів. Серед клінічних параметрів оцінювали індекс Бартела, модифікований для умов Кореї (K-MBI), індекс моторної сфери (MI) та тест мануальних функцій (MFT). Ці індекси повторно оцінювалися після періоду реабілітації. Амплітуда CMAP, викликаних стимуляцією ульнарного нерва, вірогідно корелювала з усіма клінічними показниками. Крім того, аналіз мультиваріативної лінійної регресії показав, що відношення амплітуд ульнарних CAMP є незалежним предиктором вихідного MI для верхньої кінцівки та K-MBI. Відношення амплітуд SSEP, викликаних стимуляцією медіанного нерва, було незалежним прогностичним фактором для післяреабілітаційного MI верхніх кінцівок, MFT і післяреабілітаційного K-MBI. Наші результати свідчать про те, що не тільки відношення амплітуд медіанних SSEP є прогностичним фактором щодо моторних функцій та функціонального відновлення; амплітуда ульнарних CMAP теж може бути незалежним предиктором у пацієнтів із підгострим інсультом.

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