# **Department of Rehabilitation Medicine**

Masahiro Abo, *Professor*Kazushige Kobayashi, *Associate Professor*Wataru Kakuda, *Assistant Professor*Itaru Takehara, *Assistant Professor*Tadashi Suzuki, *Assistant Professor*Keiii Hashimoto. *Assistant Professor* 

Masahiro Ohashi, Professor Kun Suk Chung, Assistant Professor Hideki Sugawara, Assistant Professor Masanori Funakoshi, Assistant Professor Nobuyuki Sasaki, Assistant Professor

#### **General Summary**

The main research topics of our department in the 2010 academic year focused on: 1) a new software program for computerized assessment; 2) basic research; 3) the Ability for Basic Movement Scale for Children (ABMS-C); and 4) repetitive transcranial magnetic stimulation (rTMS) plus occupational therapy (OT) for patients with upper limb hemiparesis after stroke and rTMS plus speech therapy for patients with aphasia after stroke.

## **Research Activities**

A new software program for computerized assessment

The objective of this study was to prove the validity and reliability of 9 of the 29 tasks of the Higher Brain Functional Balancer (HBFB), a new software program for computerized assessment. Seventy apparently healthy elderly subjects (age, 63 to 86 years; 27 men and 43 women) participated in this prospective study. The association between the Mini-Mental State Examination (MMSE) and the HBFB was tested with Pearson's correlation coefficient analysis; internal consistency of the 9 tasks of the HBFB was checked with Cronbach's coefficient alpha (Cronbach's α), and the test-retest reliability of each task was established with intraclass correlation. For test-retest reliability, 9 tasks of the HBFB were administered to the subjects twice at a 1-month interval. The test-retest HBFB quotient, data on age, length of education, and results of the MMSE were recorded. Pearson's correlation coefficient analysis showed that the state of cognitive function according to the total scores of the MMSE correlated significantly with the total quotients of the HBFB (r=0.356, p=0.002). The 9 tasks of the HBFB had appropriate internal consistency (Cronbach's  $\alpha$ =0.735). Test-retest reliability analysis indicated that the "Modified Trail Making Test," "Flashing- Light Memory," "Story," and "Route-99" tasks on the HBFB had fair-to-good reliability (intraclass correlation=0.364-0.742). However, reliability was poor with regard to the scores of the other 5 tasks. This study provides evidence for the validity of the total quotient of all tasks for the screening of total cognitive function and for the reliability of 4 of the 9 tasks from the HBFB with regard to cognitive function in elderly persons.

#### Basic research

Enterovirus 71 (EV71), a human enterovirus species A, is a major causative agent of hand, foot, and mouth disease and can also cause a wide spectrum of neurological dis-

eases. We have recently identified human P-selectin glycoprotein ligand-1 (PSGL-1) as a functional EV71 receptor and have demonstrated PSGL-1-dependent replication for some EV71 strains (PSGL-1-binding EV71 [EV71-PB]) in leukocytes. Four of 5 EV71-PB strains have replicated poorly in mouse L929 cells stably expressing human PSGL-1 (L-PSGL- 1.1 cells); therefore, we compared the replication kinetics and the entire genomic sequence of 5 original EV71-PB strains and the corresponding EV71-PB variants (EV71-LPS), which were propagated once in L-PSGL-1.1 cells. In contrast to 4 of 5 original EV71-PB strains, all EV71-LPS variants efficiently replicated and induced cytopathic effects in L-PSGL-1.1 cells in a PSGL-1-dependent manner. Direct sequence analysis of the entire genome of the original EV71-PB strains and LPS variants identified several possible adaptive mutations during the course of replication in L-PSGL-1.1 cells, including a putative determinant of the adaptive phenotype in L-PSGL-1.1 cells at VP2-149, which was shared with 4 of the 5 LPS variants. The results suggest that an adaptive mutation(s), along with a PSGL-1-binding phenotype, facilitates the efficient PSGL-1-dependent replication of EV71-PB strains in L-PSGL-1.1 cells

## Predictive validity of the new ABMS-C scale

The objective of this pilot study was to test the validity and reliability of a new scale, the ABMS-C. A total of 45 pediatric patients with disabilities (age, 0.1 to 8.8 years; 29 boys and 16 girls) participated in this prospective study. To prove the validity and reliability of the ABMS-C, it was administered to subjects at a 2-week interval. In addition to the ABMS-C score, data on age, diagnosis, and results of the Gross Motor Function Classification System were recorded. Spearman's rank correlation coefficient analysis showed that the ability to perform basic movements according to the scores of each item and the total scores of the ABMS-C correlated significantly with the levels of the Gross Motor Function Classification System (r=-0.628-0.752; p<0.001). The 5 items on the ABMS-C had appropriate internal consistency (Cronbach's  $\alpha$ =0.944). Test-retest reliability analysis indicated that the "head control," "sitting," "locomotion on flat surface," "standing," and "walking" items of the ABMS-C had almost perfect reliability ( $\kappa$ =0.865-1.000). This study provides evidence for the validity and reliability of the ABMS-C for assessing the functional ability of disabled pediatric patients.

#### Low-frequency rTMS combined with intensive OT for upper limb hemiparesis

Six-day protocol: In-hospital combination treatment was provided for 5 patients who had had upper limb hemiparesis for more than 12 months after the onset of stroke. Over 6 consecutive days, each patient underwent 10 sessions of combination treatment with 1-Hz rTMS and intensive OT (one-on-one training and self-training). Motor function in the affected upper limb was evaluated with the Fugl-Meyer Assessment (FMA), Wolf Motor Function Test (WMFT), Ten-Second Test at admission, discharge, and 4 weeks after treatment. All patients completed the 6-day treatment protocol, and none showed any adverse effects throughout the treatment. At the end of treatment, improvements in the scores of the FMA, WMFT, and Ten-Second Test were found in all patients. No deterioration of the improved upper limb function was observed 4 weeks after the end of treatment. Our proposed protocol of combination treatment appears to be safe and feasible

for patients with poststroke upper limb hemiparesis, although the efficacy of the protocol needs to be confirmed in a large number of patients.

15-day protocol: Fifteen patients (age at study entry, 55±17 years; time after stroke, 57±55 months) with poststroke upper limb hemiparesis categorized as Brunnstrom stages 3 to 5 for hand-fingers were recruited. They were considered to have reached a plateau state at study entry, based on the lack of any increase in the FMA score in the previous 3 months. During the 15-day hospitalization, each patient underwent 22 sessions of 1-Hz rTMS to the contralesional cerebral hemisphere, followed by intensive OT (one-to-one training including shaping techniques and self-training). Upper limb motor function was evaluated with the FMA and the WMFT at admission and discharge. The spasticity of finger flexors, wrist flexors, and elbow flexors in the affected upper limb was also evaluated with the Modified Ashworth Scale. The 15-day protocol was well tolerated by all patients. At discharge, the FMA score was increased in all 15 patients (from 17 to 57 points to 18 to 61 points). Shortening of performance time on the WMFT was noted in 12 patients (from 44 to 1,584 seconds to 39 to 1,485 seconds). The Modified Ashworth Scale score for some flexor muscles decreased in 12 patients. In conclusion, our 15-day protocol of low-frequency rTMS combined with intensive OT appears feasible for improving motor function and for reducing spasticity in the affected upper limb in patients with poststroke hemiparesis.

# Low-frequency rTMS combined with intensive speech therapy for aphasia

Two Japanese patients with poststroke sensory-dominant aphasia were studied. Both patients underwent 10 sessions of 20-minute low-frequency (1 Hz) rTMS to Wernicke's area during a 6-day hospitalization, followed by weekly outpatient rTMS treatment for 3 months. Language therapy was also provided through the period of inpatient and outpatient treatment. Language function was evaluated with the Token Test and the Standard Language Test of Aphasia at the start and end of inpatient treatment and the end of outpatient treatment. The therapeutic protocol was well tolerated throughout the inpatient and outpatient treatments, without any adverse effects. The scores of the Token Test and certain subcategories of the Standard Language Test of Aphasia increased in both patients after inpatient rTMS treatment. Persistent improvements of the scores were noted over the 3-month postdischarge period. The proposed protocol of long-term application of low-frequency rTMS to Wernicke's area and speech therapy is considered a safe and feasible therapeutic approach for patients with poststroke sensory-dominant aphasia.

#### **Publications**

Miyamura K, Nishimura Y, Abo M, Wakita T, Shimizu H. Adaptive mutations in the genomes of enterovirus 71 strains following infection of mouse cells expressing human P-selectin glycoprotein ligand-1. J Gen Virol 2011; 92: 287-91. Honda M (Nico Child Clin), Hashimoto K, Miyamura K, Goto H (LEDEX Corp), Abo M. Validity and reliability of a computerized cognitive assessment tool 'Higher Brain Functional

Balancer' for healthy elderly people. *Ninchi Shinkei Kagaku* 2010; **12:** 191-7.

**Kakuda W, Abo M, Uruma G, Kaito N, Watanabe M.** Low-frequency rTMS with language therapy over a 3-month period for sensory-dominant aphasia: case series of two post-stroke Japanese patients. *Brain Inj* 2010; **24:** 1113-7.

Kakuda W, Abo M, Kobayashi K, Momosaki R, Yokoi A, Fukuda A, Ishikawa A, Ito H, Tomi**naga A.** Low-frequency repetitive transcranial magnetic stimulation and intensive occupational therapy for poststroke patients with upper limb hemiparesis: preliminary study of a 15-day protocol. *Int J Rehabil Res* 2010; **33**: 339-45.

Kakuda W, Abo M, Kobayashi K, Momosaki R, Yokoi A, Ito H, Umemori T. Low-frequency rTMS combined with intensive occupational therapy for upper limb hemiparesis after brain tumour resection. Brain Inj 2010; 24: 1505-10.

Ishikawa A, Kakuda W, Taguchi K, Uruma G, Abo M. The reliability and validity of a new subjective assessment scale for poststroke upper limb hemiparesis, the Jikei assessment scale for motor impairment in daily living (in Japanese). Tokyo Jikeikai Ika Daigaku Zasshi 2010; 125: 159-67.

Yokoi A, Kakuda W, Fukuda A, Ito H, Tominaga A, Umemori T, Kameda Y, Ishikawa A, Abo M. Combination treatment of low-frequency rTMS and intensive occupational therapy for poststroke patients with upper limb hemiparesis: clinical protocol and results of neuto15 (in Japanese). Tokyo Jikeikai Ika Daigaku Zasshi 2011; 126: 79-89.

**Sawada H, Ishikawa A, Takekawa T, Kakuda W, Kawashima K, Abo M.** Botulinum toxin type a injection combined with self-training proposed by occupational therapists for spastic upper limb hemiparesis after stroke (in Japanese). *Tokyo Jikeikai Ika Daigaku Zasshi* 2011; **126:** 99-109.

Kimura A¹, Abo M, Kawate N², Osako Y³, Suyama K³, Maeda T³, Uechi Y³, Iwasaki M³ (¹Keio Univ, ²Showa Univ, ³Glaxo Smith Klein). Efficacy and safety of botulinum toxin type A in treating upper limb spasticity in post-stroke patients: a multicenter, double-blind, placebo-controlled trial followd by an open-label trial (in Japanese). Jpn J Rehabil Med 2010; 47: 714-

Kimura A<sup>1</sup>, Abo M, Kawate N<sup>2</sup>, Osako Y<sup>3</sup>, Suyama K<sup>3</sup>, Maeda T<sup>3</sup>, Uechi Y<sup>3</sup>, Iwasaki M<sup>3</sup> (<sup>1</sup>Keio Univ, <sup>2</sup>Showa Univ, <sup>3</sup>Glaxo Smith Klein). Efficacy and safety of botulinum toxin type A in treating lower limb spasticity in poststroke patients: a multicenter, double-blind, placebo-controlled trial followed by an open-label trail (in Japanese). Jpn J Rehabil Med 2010; 47: 626-36.