Neurorehabilitation of Stroke*1

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Abstract: Despite recent advances in acute stroke management, many stroke patients suffer from long-term disability. Most stroke patients regain their function partially or fully during the first 3 to 6 months depending on many factors; pre-stroke, stroke and post-stroke factors. Brain plasticity plays a major role during stroke recovery, and motor-relearning and brain plasticity shares the common mechanism. Successful neurorehabilitation is to drive beneficial plastic change and therefore to gain functional recovery. In this brief review, we will discuss mechanisms of brain plasticity engaged in stroke recovery and recent advanced management strategies for stroke recovery. (Jpn J Rehabil Med 2015 ; 52 : 63–67)

Key words: neurorehabilitation, stroke, brain plasticity

Introduction

Stroke incidence and stroke survivors are both increasing.1 Unlike other diseases, stroke remains severe impairments. According to voluntary registry data to Korean Center for Disease Control in 2012, prevalence of hemiparesis on the 7th day after stroke onset is up to 50% and more than half of them remain hemiparesis after 3 months. Thirty-one percent of stroke survivors cannot walk on the 7th day after stroke onset. A total of 49%, 23.4%, and 35% of stroke survivors have cognitive dysfunction, moderate to severe degree of dysphagia, and aphasia on the same day, respectively. The extent and duration of stroke recovery mainly depends on initial severity.2 Mildly affected patients can recover shortly, while severe patients take more than 6 months to reach recovery plateau. However, recovery after stroke depends on many variables. Stroke factors, including infarct location, size, and severity of initial stroke deficit, and premorbid factors, including age, sex, genetic polymorphism, and prestrike disability all could influence the outcome of stroke survivors. Intervention factors, including acute stroke intervention, time window for restorative therapies, amount and type of stroke therapy, medical complication after stroke, depression, and medication, are also important factors influencing stroke recovery. One of the stroke factors, intactness of corticospinal tract, was reported to be a good predictor of good functional recovery. Lee et al3 demonstrated that only 10% of patients with no response on both motor evoked potential (MEP) and sensory evoked potential (SEP) showed good functional recovery (modified Rankin scale [mRS] ≤2) compared to the patients with both MEP and SEP responses. Stroke infarct location is also an important factor for functional outcome. It was recently reported that characteristic lesion patterns in areas of motor control and areas involved in lateralized brain functions on early MRI were found to influence functional outcome using I-KNOW database (http://www.i-know-stroke.eu). Involvement of corona radiata, internal capsule, and insular cortex was a predictor for worse functional outcome in stroke patients.4

Functional neuroimaging also has been an important tool to predict stroke recovery and therefore to select appropriate individuals for successful rehabilitation. It
was shown that recovery from stroke involved sequential processes. Reperfusion is the most important treatment in hours after the onset of stroke. After that, regression of secondary changes including resolution of the ischemic penumbra, edema, and diaschisis are important for stroke recovery and brain plasticity starts to occur in days after the onset of stroke. In months after the stroke onset, training-induced reorganization is known as a significant factor for recovery.

**Very Early Rehabilitation**

Bernhardt et al. performed the first multicenter study of physical activity early after stroke. This observational study revealed that activity level was very low early after stroke onset especially at stroke unit. It was shown that during the therapeutic day within 14 days after onset, even mild stroke patients (National Institutes of Health Stroke Scale score (NIHSS) < 8) spent more than 50% of a day resting in bed, while severe stroke (NIHSS > 16) patients spending up to 95.5% of the day in bed. Based on this finding, a randomized controlled trial was conducted to evaluate the safety and feasibility of very early mobilization in post-stroke patients. The very early mobilization intervention increased the total mobilization dose to 167.0 minutes compared to the standard care group (69.0 minutes), inducing a significant decrement of time to mobilization (18.1 hours) compared to the standard care group (30.8 hours). As a result of the very early mobilization intervention, 4 to 8 times more patients showed good functional outcome (mRS < 3) at 3, 6, and 12 months later as compared to the standard care group, indicating that interventions applied in the first few weeks after stroke may improve short-term outcomes with possible long-term benefits. After this study, the American Heart Association/American Stroke Association (AHA/ASA) guideline and European stroke guideline recommended a comprehensive specialized stroke care that incorporates rehabilitation.

**Functional Recovery After Stroke**

A well-known study using anesthetized monkeys demonstrated that uninjured tissue adjacent to a cortical injury underwent functional reorganization that can be modulated by postinjury behavioral training. Functional recovery after stroke is essentially a motor relearning process with partially disrupted neural network. For example in motor network, corticospinal output has to be adequate to allow functional recovery of the motor function. Motor skill learning consists of a fast learning (significant improvements can be seen typically within a single training session) and a slow learning (further gains are achieved across multiple sessions of practice by skill retained through multiple training sessions).

Stroke recovery and brain plasticity involves genetic factors as well. It was shown that training-dependent increases in the MEP amplitude and motor map expansion were reduced in healthy subjects who had a val66met polymorphism (val66met or met66met) of the brain-derived neurotrophic factor gene (BDNF) compared to subjects without this polymorphism (val66val). This suggests that BDNF is involved in the experience-dependent plasticity of motor cortex.

Movement-related brain activation patterns after stroke were reported to be shifted from primary to secondary motor networks in both hemispheres according to severity and time course of stroke. Since secondary motor regions (such as contralesional areas) are less efficient in producing motor output, the presence of specific pattern of brain activation (including focal activity located in the ipsilesional postcentral gyrus and cingulate cortex) in the first few days after stroke predicts subsequent good motor recovery after stroke.

γ-Aminobutyric acid (GABA) is a main inhibitory neurotransmitter in brain and GABA plasticity plays an important role in stroke motor recovery. In rat stroke model, it was reported that tonic GABAergic neuronal inhibition was increased in the peri-infarct zone. In addition, reducing this excessive GABA-mediated tonic inhibition by administering in vivo benzodiazepine inverse agonist specific for GABAa receptors induced a promotion of functional recovery after stroke. To establish the mechanism of GABA neuroplasticity during the recovery phase following ischemic stroke, We assessed the changes in cerebral GABA activity using [18F]fluromazenil ([18F]FMZ) positron emission tomography (PET) and established that the change in GABA receptor availability over time was significantly associated with post-stroke motor recovery in humans. We observed that GABA activity in the peri-infarct cortex is initially increased but decreases over time during functional recovery and motor improvement.

Medications, which facilitate or impede neuroplasticity have been studied by various research groups. Am-
phentamine, t-dopa, methylphenidate, and acetylcholine agonists were known to assist stroke recovery, whereas GABA inducing drugs such as benzodiazepine, voltage-gated sodium and calcium blockers including phenytoin and phenobarbital, dopamine receptor antagonists, and alpha-2 agonists inhibit neuronal plasticity. A multicenter randomized double-blind placebo-controlled trial was conducted to prove whether fluoxetine might enhance post-stroke motor recovery when it was given to patients soon after an ischaemic stroke.\textsuperscript{20} It was found that Fugl-Meyer motor scale improvement at day 90 was significantly greater in patients who took fluoxetine than the placebo group,\textsuperscript{20} suggesting that early prescription of fluoxetine with physiotherapy might enhance motor recovery after 3 months.

Reorganization in the brain occurs during both recovery and learning but improves significantly when combined with exercises. A mice study revealed that neurogenesis in adult dentate gyrus of the hippocampus was increased under running environment condition while no improvement was shown in those just under control environment that does not promote running or exercise, indicating that exercise is the neurogenic stimulus to increase the production of new neurons.\textsuperscript{21} Meta-analysis of human studies also reported that treatment groups receiving more therapy improved more compared to the control group that received less therapy after controlling the time after the onset.\textsuperscript{22}

**Modern Concept of Rehabilitation**

The modern concept of training, task-oriented and repetitive training-based intervention using constraint-induced movement therapy (CIMT), functional electrical stimulation (FES), electromyography-triggered neuromuscular electrical stimulation, robotic interactive therapy, and virtual reality, replaced the traditional sensorimotor control training such as Brunnstrom, Bobath, Proprioceptive Neural Facilitation, and Rood method for stroke rehabilitation.

The purpose of CIMT is to avoid learned disuse of affected limb and to induce forced use of affected limb. CIMT consists of shaping exercise for the affected limb for 6 or more hours per day and constraining the intact upper limb up to 90% of waking hours over 2 weeks. A prospective single-blind randomized multisite clinical trial was conducted to compare the effectiveness of a 2-week CIMT over the usual customary care in chronic stroke patients.\textsuperscript{23} This trial first demonstrated the efficacy of rehabilitative intervention with the multicenter evidence, and took neurorehabilitative care into the area of evidence-based medicine.\textsuperscript{20} It also revealed that time after stroke does not appear to be a limiting factor for recovery.

However, a single-blind phase II trial of CIMT during acute inpatient rehabilitation performed by other group demonstrated that CIMT was equally as effective but not superior to an equal dose of traditional therapy when therapy dose was matched.\textsuperscript{24} Locomotive training with forced use and massed practice concept in lower extremities was also applied to patients after stroke.\textsuperscript{25} There was no additional benefit of body-weight supported treadmill training compared to a structured strengthening and balance exercise program for walking recovery. However, either body-weight supported treadmill training or structured program was more effective than the usual customary care at 6 months in stroke patients. Similarly, a study using robot-assisted therapy in patients with long-term upper-limb deficits after stroke demonstrated that robot-assisted therapy was not superior to intensive customary therapy.\textsuperscript{26} A recently presented prospective, multicentre, parallel-group randomized trial reported that robotic therapy could improve motor function in upper extremity in chronic stroke patients compared to the conventional therapy. However, the absolute difference between effect of robotic and that of conventional therapy was very small and of no clinical significance.\textsuperscript{27} Therefore, it is generally considered that the important factor for stroke recovery is the dose of exercise rather than the method of exercise as demonstrated in multiple studies using multiple exercise modalities as exampled above.

**Neuromodulation for Stroke Recovery**

Noninvasive brain stimulation, in the form of repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), can provide the means to modulate brain activity in a specific brain region and to induce plasticity after stroke. Other neuromodulation technique includes invasive epidural stimulation of excitatory or inhibitory protocol, somatosensory stimulation using peripherial nerve stimulations, and paired associated stimulation.\textsuperscript{28–32} We can assist stroke recovery by inhibiting competing maladaptive regions or facilitating local activity to promote desirable plastic change during practice using after-effects of these modalities. Common application of neuromodulation technique in stroke rehabilitation includes motor deficits, aphasia, neglect, dysphagia, and cognitive impairment. For example, we demonstrated that anodal tDCS applied over the affected pharyngeal motor cor-
tex enhanced the outcome of swallowing training in patients with post-stroke dysphagia, suggesting that non-invasive cortical stimulation has a potential role as an adjuvant strategy to stroke neurorehabilitation.\textsuperscript{33}

According to current knowledge, brain neuromodulation appears to be a safe and promising intervention and has a potential to be used as an adjuvant therapy for stroke rehabilitation when appropriately combined with classical behavioral therapy. However, improvement of function after brain neuromodulation is still modest, and at least network should be partially preserved for the after-effects to occur. It is unlikely that brain neuromodulation alone makes the brain form appropriate connections needed for recovery. Maybe brain neuromodulation works by strengthening existing connections or assisting the brain to form new connection. Therefore, brain neuromodulation techniques should always be accompanied by behavioral training. In the future, these neuromodulation techniques should be applied patient-specifically based on patient’s individual time course of recovery and activation pattern.\textsuperscript{34}

Conclusion

Aforementioned interventions after stroke were mainly intended to improve motor recovery. However, associated impairments are common in post-stroke patients. Hemiplegia, impairment of coordination or balance, spasticity, apraxia, neglect, behavioral problems, neurogenic bladder and bowel, deconditioning, pressure sore, depression, and pain are all common conditions after stroke. All of these conditions should be considered when treating post-stroke patients, and same principle in motor training should be applied to neurorehabilitation of these impairments. In the author’s institute, post-stroke checklist is being used according to World Congress Organization’s recommendation to improve stroke patients’ quality of life.

Neurorehabilitation of stroke has been an important issue as stroke victims are continuously increasing. Various factors are associated with recovery of stroke and researchers are continuously searching for the critical factors for neuronal recovery. Timing of initiation of rehabilitation is one of the critical factors to enhance functional restoration. Current guidelines of stroke management recommend comprehensive stroke care including rehabilitation. Current researches suggest that purposeful and intensive training is mandatory to maximize reorganization in post-stroke brain and functional restoration. Early concentrative treatment with patient-specific approach is needed in the future neurorehabilitation of stroke.

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