

## Department of Neurosurgery

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### General Summary

The research studies in our department, examining such topics as syringomyelia, endovascular surgery, mechanism of head injury, and pediatric neurosurgery, made good progress in the past year. Research in these areas is performed to international standards. Clinical research on brain tumors, hypothalamic disorders, and spine and spinal cord diseases has also continued.

### Research Activities

#### *Cerebrovascular disorders*

Although cerebral vasospasm is an important cause of morbidity and mortality in patients with subarachnoid hemorrhage (SAH), the precise mechanisms responsible for pathogenesis of cerebral vasospasm remain unclear. Recent electrophysiologic and pharmacological studies have shown the importance of potassium channels in the hyperpolarization and relaxation of vascular smooth muscle. Therefore, we have attempted to determine the role of potassium channels in the relaxation of cerebral arteries and arterioles. Recent studies suggest that functions of potassium channels are potentiated in arteries exposed to SAH and that the role of potassium channels may be more important in small arterioles than in large cerebral arteries.

In thrombolytic therapy for acute ischemic stroke, thrombolysis must be performed rapidly before ischemic neuronal injury occurs. To develop a new technique of thrombolysis for acute stroke, the effect of transcranially applied ultrasound on thrombolysis has been examined. We have reported that low-frequency and low-intensity transcranially applied ultrasound could enhance thrombolysis by tissue plasminogen activator in a rabbit model of femoral artery occlusion. Furthermore, our recent results have disclosed that ischemic neurological deficits could be reduced by transcranially applied ultrasound in a rabbit model of middle cerebral artery occlusion without an increase in the rate of hemorrhagic complications. We have reported these results in an international journal (*Stroke*). We are now attempting to confirm the safety of ultrasonification for vascular and neuronal tissue and to develop a clinically applied ultrasonication probe.

*Development of a new endovascular opening system*

We conducted several clinical and basic research studies regarding endovascular therapy.

*Development of a new endovascular operating system*

We developed a state-of-the-art endovascular neurosurgery suite that offers integrated neurosurgical and radiological capabilities. A specially designed biplane digital subtraction angiography system was installed in the neurosurgery operating room. The new suite, which facilitates three-dimensional digital subtraction angiography imaging and microsurgery, allows neurosurgeons to perform a wide array of neurosurgical and endovascular procedures.

*Development of bioactive coils (Matrix coil)*

In collaboration with the University of California Los Angeles (UCLA) School of Medicine, we developed a biodegradable, bioabsorbable polymer coil for treating brain aneurysms. This device has been approved by the United States Food and Drug Administration and been used to treat more than 30,000 patients in the United States and Europe. We are collaborating with UCLA, and the next generation of biocoils is being investigated at the Laboratory of Animal Facility.

*Development of Mebiol gel*

We have developed a thermoreversible polymer as a tissue-engineering therapeutic device. This polymer can be used as a drug delivery embolic material for treatment of malignant tumors or as a hemostatic device.

We obtained a grant for this project from the New Energy and Industrial Technology Development Organization. We have used this device to treat cerebral aneurysms, and preliminary data suggest promise for clinical application.

*Brain tumor*

In the treatment of malignant glioma, local recurrence determines the prognosis. The principal of therapy becomes the control of local recurrence. However, treating malignant glioma with chemotherapy has been difficult because the blood-brain barrier prevents chemotherapeutic agents from reaching brain tumors. To avoid these problems, a method has been developed for the local sustained release of chemotherapeutic agents by their incorporation into biodegradable polymers. Gliadel Wafer (MGI Pharma, Bloomington, MN, USA), which contains carmustine, has been authorized for the treatment of patients with malignant glioma in Europe and the United States. On the other hand, recent advances in liposome technology have shown promise because of the introduction of chemotherapeutic agents with reduced toxicity, extended longevity, and the potential for cell-specific targeting. In some previous studies, liposomal doxorubicine was used systemically to treat malignant glioma. In our study, we performed intracranial implantation of a thermoreversible polymer containing doxorubicine, a strategy that has been shown to be safe and effective for the treatment of malignant glioma. We will investigate the release kinetics, toxicity, distribution, and efficacy of this treatment *in vitro* and *in vivo*.

We have investigated the safety and effectiveness of immunotherapy with fusions of dendritic cells and glioma cells with interleukin (IL)-12 in patients with malignant glioma. The subjects were 15 patients with malignant glioma, ranging in age from 40 to 62 years. Dendritic cells were generated from peripheral blood. Cultured autologous glioma cells were obtained from surgical specimens in each case. Fusions of dendritic cells and glioma cells were prepared with polyethylene glycol. All patients received 3 to 7 immunizations with fusion cells with IL-12 at intervals of 3 weeks. Fusion cells were injected subcutaneously close to a cervical lymph node, and IL-12 was injected transvenously. There were no severe adverse effects, and two partial responses have been observed so far.

### *Neurotrauma*

Traumatic acute subdural hematomas in the Japan Neurotrauma Data Bank were categorized into a focal brain injury group and a diffuse brain injury group and were analyzed to clarify the pathophysiological and therapeutic aspects of these injuries. The analysis suggested that the pathophysiological and therapeutic aspects of acute subdural hematoma associated with diffuse brain injury differ from those of acute subdural hematoma associated with focal brain injury alone.

During the past decade neurobiochemical markers of brain damage have attracted increasing interest in neurotraumatology. The aim of this study was to investigate S-100B protein and neuron-specific enolase (NSE) as serum markers of brain cell damage after traumatic brain injury. Venous blood samples for assessing levels of S-100B protein and NSE were obtained on the day of admission and on the following day. Serum levels of S-100 protein and NSE were compared with Glasgow Coma Scale scores, computed tomographic findings, and outcomes after 3 months. Serum concentrations and kinetics of S-100B protein and NSE allow the clinical assessment of primary brain damage and the prediction of outcome after traumatic brain injury.

### *Syringomyelia*

About 50 cases of syringomyelia are surgically treated in our department each year. We have been investigating the following subjects.

1. Evaluation of the cerebrospinal fluid (CSF) obstruction at the craniovertebral junction of patients with Chiari malformation

We have been measuring the pressure volume index and outflow resistance to reveal CSF blockage, before and after surgery. The aim of this study was to determine the proper surgical procedure before the operation.

2. Electrophysiological study in patients with syringomyelia

The purpose of the surgical treatment of syringomyelia is to collapse the syrinx. However, even after the syrinx has been collapsed, some patients still have intractable pain. This pain is thought to be caused by damage to the dorsal horn of the spinal cord and is difficult to relieve. We examined sensory evoked potentials with median nerve stimulation to investigate the relation of pain relief and changes in sensory evoked potentials before and after surgery.

### 3. Fluid in the syrxinx

The mechanism of syrxinx enlargement remains unclear. The composition of syrxinx fluid is believed to be the same as that of CSF, but the origin of the fluid is unknown. We are investigating the fluid by measuring cytokine and antibiotic concentrations.

### 4. Analysis of predictive factors in patients with syringomyelia

Because of improvements in magnetic resonance imaging and neurosurgical techniques, the prognosis of patients with syringomyelia has significantly improved. However, outcomes are determined by variable preoperative conditions as well as by the surgical result. We are performing multivariate statistical analysis of predictive factors in patients with syringomyelia.

### *Pediatric neurosurgery*

The Division of Pediatric Neurosurgery, The Jikei University Hospital Women's and Children's Medical Center, was established in October 2002. In the last 6 years, we have collected more than 1,000 new cases of various entities, including hydrocephalus (27%), spina bifida (25%), brain tumors (13%), and craniofacial anomaly (8%). Since April 2003, the clinical research fellows, 12 from other domestic universities and 9 from other countries (including Germany, Italy, Austria, Jordan, and Bulgaria) have taken part in our research activities.

In hydrocephalus research, we have performed pathophysiological analyses of CSF dynamics, both in fetal and postnatal periods, along with extensive clinical investigations in a large series of cases. On the basis of the results we have proposed a new theory for the specificity of CSF dynamics in the immature brain, i.e., "Evolution Theory in CSF Dynamics."

We have also completed the development of a new neuroendoscope and proposed a new surgical technique (J Neurosurg : 102, 2005) and a specific technique for treating intracranial cyst (J Neurosurg : 103, 2005), with a specific navigational endoscope trajectory called the "Oi clear Navi Sheath" (J Neurosurg : 07, 2007). We have been assembling the largest series of patients. A member of our department has been nominated as chairman for the National Study Group on Spina Bifida and Conducting nationwide and international cooperative studies on controversial issues in this field.

In craniofacial anomaly research, we have extensively applied the distraction method for Japan's largest series of cases; the clinical efficiency has been summarized, and our extensive study received the honorable prize of the International Society for Pediatric Neurosurgery, Raimondi's Award in 2004, and the Kawabuchi Award in 2005.

Our clinical and research activities have been also well maintained both in Tokyo (JWCMC: Jikei University Women's & Children's Medical Center) and Hannover, Germany (the International Neuroscience Institute) on the basis of firm international collaboration exchanging leading pediatric neurosurgeons and related research workers. Our department has continued as the headquarters of the International Study Group on Neuroendoscopy, the Japanese Society for Pediatric Neurosurgery, the Japan Academy of Hydrocephalus Research, as well as the Presidency of the Executive Board Committee of the International Society for Pediatric Neurosurgery, and the Japan Association of Medical English Education) as the President in each Executive Board.

*Spine and spinal cord*

Numerous conditions, including syringomyelia, degenerative spine diseases, spinal cord tumors, and spinal vascular lesions, have been the major concerns of our department. The departments of orthopedic surgery and neurosurgery often collaborate in the interests of patient-orientated treatment in our hospital.

As a clinical research activity, the analysis of pain in patients with neuropathic pain has started. The Dyna CT scanning system in operating rooms 4 and 5 seems to be one of the most sophisticated and unique image-guided surgery systems, especially when used with a navigation system.

Basic research, including research on spinal cord injuries and regeneration technology, has just begun in our group.

*Hypothalamopituitary disease*

In 1995, we developed the endoscopic endonasal transethmoidal technique, a new operative approach for parasellar diseases, in collaboration with otolaryngologists. Using this method, developed on the basis of the theory and practice of functional endoscopic sinus surgery, we use only an endoscope without a nasal speculum to go through ethmoid sinuses via the nostril to reach the sphenoid sinus. Thereafter, we have continued to improve the safety and effectiveness of our operative method by introducing a navigation system for nasal sinus surgery and developing surgical instruments. Now we are working to establish technical standards in collaboration with several other institutions.

Numerous therapeutic drugs for hormone-producing pituitary adenomas are being developed. The standard treatment for prolactinomas is pharmacotherapy with bromocriptine, terguride, and cabergoline, but definitive criteria for treatment selection have not been established. We studied the relation between the results of drug-loading tests and therapeutic effects, performed a long-term analysis of many cases, and studied the problems of pharmacotherapy. These studies should prove useful for establishing criteria for treatment selection in pharmacotherapy for prolactinoma.

We investigated the mechanism of action of a somatostatin analogue for growth-hormone-producing pituitary adenoma and clarified one part of the mechanism of action.

**Publications**

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