

Department of Neurosurgery

Toshiaki Abe, *Professor*
Shizuo Oi, *Professor*
Satoshi Tani, *Professor*
Hisashi Onoue, *Associate Professor*
Yuzuru Hasegawa, *Assistant Professor*
Tatsuhiro Joki, *Assistant Professor*

Haruo Sakai, *Professor*
Yuichi Murayama, *Professor*
Satoshi Ikeuchi, *Associate Professor*
Masato Nakajima, *Assistant Professor*
Yoshiaki Miyazaki, *Assistant Professor*
Yasuko Kusaka, *Assistant Professor*

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

Although cerebral vasospasm is a major cause of morbidity and mortality in patients with subarachnoid hemorrhage (SAH), precise mechanisms responsible for the pathogenesis of cerebral vasospasm remain undefined. Recent electrophysiologic and pharmacological studies show that potassium channels play important roles 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. The recent results suggest that the 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, it is essential to achieve thrombolysis before ischemic neuronal injury occurs. To develop a new technique of thrombolysis after 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 can enhance thrombolysis by tissue plasminogen activator in a rabbit model of femoral artery occlusion. Furthermore, our recent results show that ischemic neurological deficits can 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 ultrasonication for vascular and neuronal tissue and to develop a clinically-applied ultrasonication probe.

Development of a new endovascular opening system

We performed 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. In May 2008, robotic digital subtraction angiography system, Zeego by Siemens, was installed in our operating suite. The new suite, which has 3-dimensional digital subtraction angiography imaging and microsurgery capabilities, allows neurosurgeons to perform a wide array of neurosurgical and endovascular procedures.

Development of bioactive coils (Matrix coil)

We developed a biodegradable, bioabsorbable polymer coil for the treatment of brain aneurysms at University of California Los Angeles (UCLA) School of Medicine. This device has been approved and has been used to treat more than 30,000 patients in the United States, Europe, and Japan. We are collaborating with UCLA, and the next generation of bioactive coil is being investigated at the Jikei Animal Laboratory. We are planning new clinical research for the treatment of unruptured intracranial aneurysms.

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 the 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 hold promise for clinical application.

Flow dynamics for intracerebral aneurysm

The aim of this project was to predict the risk of rupture of untreated cerebral aneurysms and to develop next-generation therapies that can be used to modify the flow dynamics of the aneurysms. In collaboration with Waseda University, we established a new variable, "energy loss," which can be used to predict aneurysm rupture. In addition we developed a new computational software program that can be used to measure aneurysm size and volume immediately using 3-dimensional information. This software will be commercially available soon.

Brain tumor

In the therapy of malignant glioma, local recurrence often determines prognosis. The principal of therapy thus becomes the control of local recurrence. However, treating local recurrence with chemotherapy is difficult because the blood-brain barrier is a major obstacle preventing chemotherapeutic drugs from reaching brain tumors. To overcome these problems, a method has been developed for the local sustained release of chemotherapeutic agents by their incorporation into biodegradable polymers. In our study we try to use doxorubicine within thermoreversible polymer for intracranial implantation, a strategy that has been shown to be safe and successful in the treatment of malignant

gliomas. We will investigate the release kinetics, toxicity, distribution, and efficacy of this preparation *in vitro* and *in vivo*.

We investigated the safety and clinically effect of immunotherapy with fusions of dendritic 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 the 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 serious adverse effects, and partial responses have been observed in 2 patients.

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 pathophysiological and therapeutic aspects of acute subdural hematoma associated with diffuse brain injury appear to differ from those with focal brain injury alone.

During the past decade neurobiochemical markers of brain damage have attracted increasing attention 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 measurement of S-100B protein and NSE were obtained after admission and the following day. Serum levels of S-100 protein and NSE were compared with the Glasgow Coma Scale score, computed tomographic findings, and outcome after 3 months. Serum concentration and kinetics of S-100B protein and NSE allow the clinical assessment of primary brain damage and have predictive value for outcomes after traumatic brain injury.

Syringomyelia

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

1. Evaluation of the cerebrospinal fluid obstruction at the craniovertebral junction in patients with Chiari malformation

We have been measuring the pressure volume index and out-flow resistance to reveal cerebrospinal fluid (CSF) blockage, before and after surgery. The aim of this study is to determine the proper surgical procedure prior to the operation.

2. Electrophysiological research in patients with syringomyelia

The goal of the surgical treatment of syringomyelia is to collapse the syrinx. However, even after this goal has been achieved, some patients still have intractable pain. This pain, which is thought to be caused by damage to the dorsal horn of the spinal cord, is difficult to relieve. We examined somatosensory evoked potentials with median nerve stimulation to reveal the correlation of pain relief and alterations in somatosensory evoked potentials before and after surgery.

3. Fluid in the syrx

The mechanism of syrx enlargement remains unclear. The content of the syrx is believed to be CSF, but where and how the fluid originates are unknown. We are researching the fluid by measuring cytokine and antibiotic concentrations.

4. Analysis of predictive factors in syringomyelic patients

With the introduction of magnetic resonance imaging and advances in neurosurgical techniques, outcomes of patients with syringomyelia have improved significantly. However, the outcomes are determined not only by the surgical result but also by various preoperative conditions. We are using multivariate statistical analysis to examine predictive factors in patients with syringomyelia.

Pediatric neurosurgery

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

In the field of hydrocephalus research, pathophysiological analyses of CSF dynamics in both the fetal and postnatal periods have been extensively investigated (J Neurosurg 106: 2006). On the basis of these large clinical series with extensive clinical investigations, we have proposed a unique theory for the specificity of CSF dynamics in immature brain, namely "Evolution Theory in CSF Dynamics" (Childs Nerv Syst 22: 2006).

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 intracranial cyst (J Neurosurg: 103, 2005). We have been collecting the largest series of patients and have developed other related new instruments (J Neurosurg 106: 2006).

A member of our department has been nominated as the chairman of the National Study Group on Spina Bifida and has been promoting further nationwide and international cooperative studies on controversial issues in this field. In the field of craniofacial anomaly research, we have extensively applied the distraction method to Japan's largest series of cases; the clinical efficacy has been summarized, and our extensive work received the honorable prize of the International Society for Pediatric Neurosurgery, Raimondi's Award in 2004, the Kawabuchi Award in 2005, the Bhagwati Oration in 2006, and the Joon-Ki Kang Lecture in 2006.

Our clinical and research activities have been well maintained both in Tokyo (The Jikei University Hospital Women's & Children's Medical Center) and in Hannover, Germany (the International Neuroscience Institute) on the basis of firm international collaboration with world-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, and a member of our department has served as the President of the Executive Board Committee of the International Society for Pediatric Neurosur-

gery and the Japan Association of Medical English Education.

Spine and spinal cord group

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.

In clinical research, new devices for anterior cervical interbody fusion and cervical laminoplasty have been developed, and their efficacy has been proven. The Artis Zeego system (Siemens), newly installed in operating room 5, with a navigational system, offers one of the most sophisticated and unique image-guided surgery systems in the world. Basic research, including research on spinal cord injury and regeneration technology, has just begun in our group.

Hypothalamopituitary disease

The endoscopic biendonasal transthemosphenoïdal approach, a new surgical technique for sellar and parasellar diseases which we developed, was established as an approved operative procedure. With this method, we use only an endoscope without any nasal speculum. We have performed more than 170 operations and have proceeded with the introduction of a navigation system for nasal surgery and special surgical instruments. We are now trying to find a safer route of approach.

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.

Furthermore, we are investigating ACTH precursors that are produced by subclinical ACTHomas.

Publications

Arai T, Takahashi-Fujisaki J, Joki T, Nagashima H, Ichiba N, Kawakami M, Abe T. Volumetric analysis of a rhabdoid meningioma during preoperative follow-up: ba case report. *Acta Neurol Belgica* 2008; **108**: 112-5.

Takao H, Murayama Y, Ebara M, Ishibashi T, Saguchi T, Irie K, Yoshioka H, Mori Y, Vinuela F, Abe T. New thermoreversible liquid embolic agent for embolotherapy: technical report. *Neuroradiology* 2009; **51**: 95-8.

Terao T, Yokochi F, Kawasaki T, Okiyama R,

Hamada T, Nishikawa N, Izawa N, Shin M, Kumada S, Takahashi H. Microelectrode findings and topographic reorganisation of kinaesthetic cells after gamma knife thalamotomy. *Acta Neurochir* 2008; **150**: 823-7.

Tanaka A, Abe T. Therapeutic efficacy of STI-571, c-kit tyrosine kinase inhibitor, used in combination with TNP-470, an angiogenesis inhibitor, in the treatment of glioma. *Jikeikai Med J* 2008; **55**: 1-6.

Shimizu J, Matsumoto M, Yamazaki E, Yasue M.

Spontaneous regression of an asymptomatic meningioma associated with discontinuation of progesterone agonist administration: case report. *Neurol Med Chir* 2008; **48**: 227-30.

Kajiwara I, Tanaka T, Kan I, Ohtsuka T, Sawautchi S, Murakami S, Abe T. Intracystic hematoma of middle fossa arachnoid cyst caused by ruptured of internal carotid-posterior communicating artery aneurysm. *Neurol Med Chir* 2008; **48**: 220-2.

Akiyama M, Tateshima S, Hasegawa Y. Cortical laminar necrosis caused by critically increased intracranial pressure in infant: case report. *Neurol Med Chir* 2008; **48**: 326-9.

Ishibashi T, Mirayama Y, Urashima M, Saguchi T, Ebara M, Arakawa H, Irie K, Takao H, Abe T. Unruptured intracranial aneurysms incidence of rupture and risk factors. *Stroke* 2009; **40**: 313-6.