

Department of Neurosurgery

Toshiaki Abe, *Professor*
Shizuo Oi, *Professor*
Yuichi Murayama, *Professor*
Hisashi Onoue, *Associate Professor*
Yoshiaki Miyazaki, *Assistant Professor*
Yasuko Kusaka, *Assistant Professor*
Toshihiro Ishibashi, *Assistant Professor*

Haruo Sakai, *Professor*
Satoshi Tani, *Professor*
Satoshi Ikeuchi, *Associate Professor*
Yuzuru Hasegawa, *Associate Professor*
Tatsuhiro Joki, *Assistant Professor*
Toshihide Tanaka, *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

Cerebrovascular Disorders

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.

Endovascular surgery

1. Development of a new endovascular opening system

We performed several clinical and basic research studies related to endovascular therapy.

2. 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, a robotic digital subtraction angiography system (Zeego, Siemens Medical Systems, Erlangen, Germany) 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.

3. 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.

4. 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.

5. 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 treatment 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. Gliadel Wafer (Eisai Co., Ltd., Tokyo, Japan), which contains carmustine, has been authorized in Europe and the United States and is used for the patients with malignant glioma. On the other

hand, recent advances in liposome technology have shown promise for the introduction of chemotherapeutic agents with reduced toxicity, extended longevity, and potential for cell-specific targeting. In some previous reports, liposomal doxorubicine was used systemically to treat malignant glioma. In our study we have tried to use doxorubicine and a proteasome inhibitor (MG132) within a 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 effects of immunotherapy with fusions of dendritic and glioma cells in patients with malignant glioma. 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 at intervals of 3 weeks. Fusion cells were injected subcutaneously close to a cervical lymph node. There were no serious adverse effects, and partial responses have been observed in 2 patients.

Neurotrauma

Few institutions have engaged in research on neurotraumatology. A unique aspect of our department is research in this area, which has 3 major topics. We examined the prevalence of sports-related head injury in collaboration with the Japan Society of Clinical Sports Medicine and the Japan Society of Neurotraumatology. We also examined sports-related concussion and performed mechanical studies of head-injury through simulations.

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.

In syringomyelia related to Chiari malformation, the relation between cerebrospinal fluid (CSF) circulation blockage and cavitation of the spinal cord has been clarified. Therefore, the improvement of the CSF circulation becomes the goal of surgical treatment. However, the mechanism of cavitation of the spinal cord is not fully understood. In patients with Chiari malformation, the cerebellar tonsils and the ventral vector (i.e., the dens) compress the spinal cord and restrict CSF circulation. We examined whether these 2 factors influence the effects of foramen magnum decompression.

2. Fluid in the syrinx

The mechanism of syrinx enlargement remains unclear. The content of the syrinx 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.

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 depart-

ment. The departments of orthopedic surgery and neurosurgery often collaborate in the interests of patient-orientated treatment in our hospital.

In clinical research, an analysis of pain in patients with neuropathic pain was started. The DynaCT scanning system (Siemens Medical Systems) in operating rooms 4 and 5 is one of the most sophisticated image-guided surgery systems, especially when paired with a navigation system.

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

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 10 years more than 1,500 new cases of various entities have been collected and recorded in our data bank, including, spina bifida, hydrocephalus, craniofacial anomalies, and brain tumors. Since April 2003, 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 the field of hydrocephalus research, pathophysiological analyses of CSF dynamics in both the fetal and postnatal periods have been extensively investigated. 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 the 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 cysts (*J Neurosurg*: 103, 2005) with a specific navigational endoscope trajectory as "Oi clear Navi Sheath" (*J Neurosurg*: 107, 2007). We have been collecting the largest series of patients.

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, and the Kawabuchi Award in 2005.

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.

Publications

Akasaki Y, Kikuchi T, Irie K, Yamamoto Y, Arai T, Tanaka T, Joki T, Abe T. Cotransfection of Poly (I : C) and siRNA of IL-10 into fusions of den-

drific and glioma cells enhances antitumor T helper type 1 induction in patients with glioma. *J Immunother* 2011; **34**: 121-8.

Arai T, Benny O, Joki T, Menon LG, Machluf M, Abe T, Carroll RS, Black PM. Novel local drug system using thermoreversible gel in combination with polymeric microspheres or liposomes. *Anticancer Res* 2010; **30**: 1057-64.

Ishii T, Terao T, Komine K, Abe T. Intramedullary spinal cord metastases of malignant melanoma: an autopsy case report and review of the

literature. *Clin Neuropath* 2010; **29**: 334-40.

Takao H, Murayama Y, Ishibashi T, Saguchi T, Ebara M, Arakawa H, Irie K, Iwasaki K, Umezu M, Abe T. Comparing accuracy of cerebral aneurysm size measurements from three routine investigations: computed tomography, magnetic resonance imaging, and digital subtraction angiography. *Neurol Med Chir* 2010; **50**: 893-9.