Department of Neurosurgery

Yuichi Murayama, *Professor*
Takaaki Yanagisawa, *Professor*
Hisashi Onoue, *Associate Professor*
Tatsuhiro Joki, *Associate Professor*
Nobuyoshi Kaito, *Assistant Professor*
Tosihide Tanaka, *Assistant Professor*
Akira Ishoshima, *Assistant Professor*
Ichiro Yuki, *Assistant Professor*
Hideki Arakawa, *Assistant Professor*
Satoshi Tani, *Professor*
Satoshi Ikeuchi, *Associate Professor*
Yuzuru Hasegawa, *Associate Professor*
Toshihiro Ishibashi, *Associate Professor*
Hiroyasu Nagashima, *Assistant Professor*
Yasuharu Akasaki, *Assistant Professor*
Toru Terao, *Assistant Professor*
Takao Arai, *Assistant Professor*
Yuichiro Nonaka, *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 diseases・Endovascular surgeries

1. Analysis on the natural history of unruptured intracranial aneurysms

Since 2003, more than 3,000 patients with intracranial aneurysms have visited our department. As one of the world's leading aneurysm treatment centers, The Jikei University has placed a great value on establishing a precise real-time database of patients with aneurysms.

We focused on the analysis of: 1) the natural history of unruptured aneurysms, 2) risk factors associated with the rupture of aneurysms, and 3) risk factors associated with treatment. We are now analyzing the data and aim to publish these data in several neurosurgical journals.

2. Analysis of biofluid mechanics on human intracranial aneurysms using a computational fluid dynamics

Owing to research in collaboration with the Tokyo University of Science, we have been making numerous contributions regarding the biofluid mechanics of brain aneurysms using computational fluid dynamics analysis. The research collaboration has been steadily expanding, and several international collaborative studies are now in progress. The main topics of our current studies include: 1) development of novel variables, 2) clarifying the relationship between hemodynamic patterns and the risk of rupture, and 3) development of dedicated software for computational fluid dynamics for angiography workstations.

3. Development of novel imaging software for the analysis of cerebrovascular disease

To improve the image quality of current modalities, e.g., magnetic resonance, computed tomography (CT), and angiography, several types of image-processing software are under development. The prototype of a novel software program to remove metal artifacts from

C-arm CT images has been installed in our animal laboratory. By significantly reducing artifacts due to metal coils, this software has significantly improved visualization near the coil mass in C-arm CT images. The results of the data analysis were recently published in the *American Journal of Neuroradiology* (in press).

The software has recently become commercially available for angiography devices built by Siemens Medical Systems (Erlangen, Germany). The clinical data is now being investigated and will be reported some time 2015.

Other software programs, such as *syngo* PBV Neuro (for measuring cerebral blood volume during angiography), and a high-resolution C-arm CT are also commercially available. The collected data is now being analyzed, and the results are expected to be reported at the annual conference of the Neurosurgical Association and the Japanese Society of Neuroendovascular Therapy in 2015.

A new software program called 4-dimensional digital subtraction angiography has recently become available for angiography workstations. The new software provides high spatial resolution and temporal resolution at the same time in a single acquisition. We have already performed this software for more than 60 patients and discovered that it is extremely useful, especially for patients with vascular malformation, for example, arteriovenous malformations and dural arteriovenous fistulas.

4. Development of a novel intracranal stent device for the treatment of brain aneurysms

A novel intracranial stent device for treating brain aneurysms is being developed. The novel stent device has a very low profile delivery system (compatible with a 2.1-Fr system) and functions as a flow-diverter device but can still be used for stent-assisted coil embolization.

A preclinical animal study is in progress. This project is supported by a research grant from the Ministry of Economy, Trade and Industry for more than ¥50 million over 5 years. We are now in the final stage of consecutive experiments, and the results will be reported to the Ministry of Economy, Trade and Industry in February 2016.

5. Development of novel bioactive coil device for the treatment of brain aneurysms

The Matrix Detachable Coil System was introduced to the market in 2002 as a first-generation bioactive coil material for treating aneurysms. This device has been used for more than 70,000 patients throughout the world, and now a second generation of bioactive coils is being developed. The results of animal experiment have been promising, and preclinical animal studies are now in progress.

6. Establishment of a telemedicine network utilizing a novel software for smartphones

After the successful introduction of the mobile telemedicine software program "i-stroke," the quality of stroke care in our institution has been dramatically changed. Now, "Join," the next generation of telemedicine software, is available for any smartphone user. The application allows all medical staff to have instant access to the picture archiving and communication system in The Jikei University Hospital and allows the staff to communicate with an online bulletin board system. The application has been released in collaboration with NTT Docomo, which is Japan's largest mobile service provider, with more than 60 million customers.

Brain tumor

1. Immunotherapy against malignant glioma

Effective antigen presentation to T cell subsets, such as CD8+ and CD4+ T cells, is a critical step in the generation and maintenance of immune responses against cancer cells. Although several cell types have the ability to present antigens, this function is performed most efficiently by professional antigen-presenting cells, of which dendritic cells (DCs) are the most potent.

After exposure to tumor-associated antigens (TAAs), DCs process and express TAA-derived epitopes in combination with MHC class I and II molecules on their cell surfaces and induce TAA-specific cytotoxic T-lymphocyte and T-helper type 1 subsets, respectively. We have previously shown that immunotherapy for glioma with fusions of DCs and glioma cells induces safe, tumor-specific immune responses. In a recent study, we observed that polyinosinic:polycytidylic acid (Poly[I:C]) transfection induced high levels of interleukin (IL) 12 secretion from FCs. We also found that the ability of Poly(I:C)-transfected FCs to produce IL-12 was preserved when endogenous IL-10 was suppressed by small interference RNA (siRNA) of IL-10 (IL-10-siRNA) and that FCs cotransfected with IL-10 siRNA and Poly(I:C) elicited an efficient tumor-specific T-helper type 1 response. At the 73rd annual meeting of the Japan Neurosurgical Society and the 32st annual meeting of the Japan Society for Neuro-Oncology, we reported that cotransfection of Poly(I:C) and IL-10 siRNA into fusions of DCs and tumor cells is a practical strategy to enhance antitumor responses. The FC immunotherapy is now in a process to receive approval from the Ministry of Health, Labor and Welfare as an advanced medical treatment.

2. Establishment of the Brain Tumor Bank

We established a system to preserve the tissue of brain tumors with a refrigeration named the Brain Tumor Bank. The frozen tissues will be analyzed with a recently developed next-generation DNA sequencing system that allows us to sequence DNA and RNA much more quickly and inexpensively than with the previously used Sanger sequencing system. These studies will help develop a new diagnostic procedure and novel therapy in the future.

Study of intraoperative imaging with C-arm CT-

We use a C-arm CT, *syngo* DynaCT system (Siemens Medical Systems), and an image-analysis software program for metal-artifact reduction in the surgical resection of brain tumors. Intraoperative imaging with this system helps increase the resection rate of tumors with a surgical navigation system and photodynamic diagnosis with 5-aminolevulinic acid. The purpose of this study is to establish safe technical innovations for the surgical resection of brain tumors.

Neurotrauma

Few institutions have performed research in neurotraumatology. A unique aspect of our department is that we have undertaken 3 major studies in this area of research. 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 have also

examined sports-related concussion and performed mechanical studies of head injury through simulations.

Syringomyelia
About 50 patients with syringomyelia are treated surgically in our department each year. By evaluating cerebrospinal fluid (CSF) obstruction at the craniovertebral junction in patients with syringomyelia related to Chiari malformation, the relation between CSF circulation blockage and cavitation of the spinal cord has been clarified. Therefore, improving 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., dens) compress the spinal cord and restrict CSF circulation. We examined whether these 2 factors influence the effects of foramen magnum decompression.

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

Division of Pediatric Neurosurgery
The Division of Pediatric Neurosurgery performs operations for patients with spina bifida, myeloschisis, spinal lipoma, hydrocephalus caused by various medical conditions, cranial facial anomaly, and brain tumor and follows them up postoperatively at the outpatient clinic. In the last 10 years we have treated more than 1,700 new cases of various entities. We currently consist of a consultant, a division staff, and a resident and promote clinical research through various clinical activities.
For spina bifida, we are currently examining the prognosis of neurological functions by operating under neuromonitoring. We are also developing operative procedures for hydrocephalus using neuroendoscope and proposing the usage of navigation systems.
Our clinical research for craniosynostosis surgery, in collaboration with the Department of Plastic and Reconstructive Surgery, has developed operative procedures using distraction method depending on different age and has received the honorable prize of the International Society for Pediatric Neurosurgery, Raimondi's Award, in 2004 and the Kawabuchi Award in 2005.

Publications

Hetts SW, Turk A, English JD, Dowd CF, Mocco J, Prestigiacomo C, Nesbit G, Ge SG, Jin JN, Carroll K, Murayama Y, Gholkar A, Barnwell S, Lopes D, Johnston SC, McDougall C; Matrix and Platinum Science Trial Investigators. Stent-assisted coiling versus coiling alone in unruptured intracranial aneurysms in the matrix and platinum science trial: safety, efficacy, and mid-term outcomes. *AJNR Am J Neuroradiol*. 2014; **35:** 698-705.

Mori R, Joki T, Nonaka Y, Ikeuchi S, Abe T. Parallel Insertion endoscopic technique for precise catheter placement in cystic craniopharyngiomas. *J Neurol Surg A Cent Eur Neurosurg*. 2014; **75:** 442-6.

Fujimoto M, Takao H, Suzuki T, Shobayashi Y, Mayor F, Tateshima S, Yamamoto M, Murayama Y, Viñuela F. Temporal correlation between wall shear stress and in-stent stenosis after Wingspan stent in swine model. *AJNR Am J Neuroradiol*. 2014; **35:** 994-8.

Kobayashi N, Murayama Y, Yuki I, Ishibashi T, Ebara M, Arakawa H, Irie K, Takao H, Kajiwara I, Nishimura K, Karagiozov K, Urashima M. Natural course of dissecting vertebrobasilar artery aneurysms without stroke. *AJNR Am J Neuroradiol*. 2014; **35:** 1371-5.

Yuki I, Spitzer D, Guglielmi G, Duckwiler G, Fujimoto M, Takao H, Jahan R, Tateshima S, Murayama Y, Viñuela F. Immunohistochemical analysis of a ruptured basilar top aneurysm autopsied 22 years after embolization with Guglielmi detachable coils. *J Neurointerv Surg*. 2015: **7**: e29. Epub 2014 Jul 25.

Mori R, Cavavllo LM, Guadagno E, Imperato A, Murayama Y, Cappabianca P. Extracranial spheno-ethmoidal sinus menigioma: case report. *Truk Neurosurg*. 2014; **24:** 788-92.

Sato K, Tanaka T, Kato N, Ishii T, Terao T, Murayama Y. Metastatic cerebellar gastrointestinal stromal tumor with obstructive hydrocephalus arising from the small intestine: a case report and review of the literature. *Case Rep Oncol Med*. 2014; **2014**: 3431782014.

Fukuoka K, Yanagisawa T, Suzuki T, Shirahata M, Adachi J, Mishima K, Fujimaki T, Matsutani M, Nishikawa R. Malignant transformation of germinoma 14 years after onset: favorable efficacy of oral etoposide. *Pediatr Int*. 2015; **57:** 483-6. Epub 2015 Feb 24.

Tanaka T, Kato N, Hasegawa Y, Murayama Y. Unpredicted sudden death due to recurrent infratentorial hemangiopericytoma presenting as massive intratumoral hemorrhage : A case report and review of the literature. *Case Rep Neurol Med*. 2014; **2014**: 230681.

Sato I, Higuchi A, Yanagisawa T, Mukasa A, Ida K, Sawamura Y, Sugiyama K, Saito N, Kumabe T, Terasaki M, Nishikawa R, Ishida Y, Kamibeppu K. Cancer-specific health-related quality of life in children with brain tumors. *Qual Life Res*. 2014; **23:** 1059-68.

Fukushima S, Otsuka A, Suzuki T, Yanagisawa T, Mishima K, Mukasa A, Saito N, Kumabe T, Kanamori M, Tominaga T, Narita Y, Shibui S, Kato M, Shibata T, Matsutani M, Nishikawa R, Ichimura K; Intracranial Germ Cell Tumor Genome Analysis Consortium (iGCT Consortium). Mutually exclusive mutations of KIT and RAS are associated with KIT mRNA expression and chromosomal instability in primary intracranial pure germinomas. *Acta Neuropathol*. 2014; **127:** 911-25.

Fukuoka K, Yanagisawa T, Suzuki T, Shirahata M, Adachi J, Mishima K, Fujimaki T, Matsutani M, Nishikawa R. Duration between onset and diagnosis in central nervous system tumors: Impact on prognosis and functional outcome. *Pediatr Int*. 2014; **56:** 829-33.

Fukuoka K, Yanagisawa T, Watanabe Y, Suzuki T, Shirahata M, Adachi J, Mishima K, Fujimaki T, Matsutani M, Wada S, Sasaki A, Nishikawa R. Brainstem oligodendroglial tumors in children: two case reports and review of literatures. *Childs Nerv Syst*. 2015; **31:** 449-55.

Sato I, Higuchi A, Yanagisawa T, Murayama S, Kumabe T, Sugiyama K, Mukasa A, Saito N, Sawamura Y, Terasaki M, Shibui S, Takahashi J, Nishikawa R, Ishida Y, Kamibeppu K. Impact of late effects on health-related quality of life in survivors of pediatric brain tumors: motility disturbance of limb(s), seizure, ocular/visual impairment, endocrine abnormality, and higher brain dysfunction. *Cancer Nurs*. 2014; **37**(6): E1-14.

Irie K, Yanagisawa T, Hasegawa Y, Takeishi H, Ohashi S, Yamamoto Y, Tochigi S, Tanaka T, Murayama Y. Endovascular embolization of ruptured subependymal artery aneurysm associated with moyamoya disease: a case report (in Japanese). *JNET: Journal of Neuroendovascular Therapy*. 2014; **8:** 266-72.

Arai T, Hasegawa Y, Tanaka T, Kato N, Watanabe M, Nakamura A, Murayama Y. Transient Chales Bonnet syndrome after excision of a right occipital meningioma : a case report (in Japanese). *Neurological Surgery*. 2014; **42:** 445-51.