

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 diseases · Endovascular surgeries

1. Analysis of the natural history of unruptured intracranial aneurysms

Since 2003, more than 4,000 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 in human intracranial aneurysms using computational fluid dynamics

Owing to the research 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 imaging software for analyzing 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, and the quality of the

images is being analyzed. By significantly reducing artifacts due to metal coils, this software has significantly improved visualization near the coil mass in C-arm CT images. The software has recently become commercially available for angiography devices built by Siemens Medical Systems (Erlangen, Germany). 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.

4. Development of a novel intracranial stent device for treating 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 (2.1 Fr system compatible) 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.

5. Development of a novel bioactive coil device for treating 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 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 users. 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 using an online bulletin board system. The application has been released in collaboration with NTT Docomo, which is the Japan’s largest mobile service provider, with more than 60 million customers.

Brain tumor

The current therapeutic standard for malignant glioma includes surgery followed by concomitant radiation and chemotherapy with temozolomide. The median survival time of patients with glioblastoma multiforme, the glioma with the highest grade of malignancy, is 15 months, despite aggressive treatment with surgical resection, radiotherapy, and temozolomide chemotherapy. Although the cytotoxic effect of temozolomide correlates with epigenetic silencing of the *MGMT* gene by promoter methylation in tumor cells, there are few therapeutic options for patients with temozolomide-resistant glioma. A novel therapy to improve the prognosis of patients with temozolomide-resistant glioma is, therefore, eagerly awaited, and “chemoimmunotherapy,” a synergism of chemotherapy and immunotherapy, is one such novel paradigm that has been investigated for different types of tumors, including 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. As the efficient isolation and preparation of human and murine DCs have become possible, the strategies to elicit effective uptake of TAAs by DCs have gained special interest for developing novel cancer immunotherapies. We have previously shown in a phase 1 clinical trial that immunotherapy for glioma with fusions of DCs and glioma cells induces safe, tumor-specific immune responses. The therapeutic significance of recombinant interleukin (IL)-2 supplementation in fusion cell (FC) immunotherapy has also been shown in a phase 2 clinical trial. A strategy to induce high levels of IL-12 production by FCs might thus enhance the antitumor responses in FC immunotherapy. In another study, we observed that polyinosinic: polycytidylic acid (Poly[I:C]) transfection induced high levels of 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 31st 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. FC immunotherapy has been submitted to the Ministry of Health, Labour and Welfare for approval as an advanced medical treatment.

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, The Jikei University Hospital Women's & Children's Medical Center was established in October 2002. In the last 10 years we have treated more than 1,500 new cases of various entities, including, spina bifida, hydrocephalus, craniofacial anomalies, and brain tumors. Now our division has been run by three staffs since 2012.

In the field of hydrocephalus research, extensive pathophysiological analyses of CSF dynamics have been performed in both the fetal and postnatal periods. On the basis of these large series of clinical cases with extensive clinical investigations, we have proposed a unique theory for the specificity of CSF dynamics in the immature brain. We have also completed the development of a new neuroendoscope and have proposed a new surgical technique with or without the use of a neuronavigation system.

We have been collecting the largest series of patients with spina bifida. We have been promoting national 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 of this method has been summarized, and our extensive work has 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 also been well maintained on the basis of firm international collaboration with world-leading pediatric neurosurgeons and related researchers.

Publications

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Reviews and Books

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