

## Department of Internal Medicine

### Division of Neurology

---

Yasuyuki Iguchi, *Professor*  
Akira Kurita, *Associate Professor*  
Masahiko Suzuki, *Assistant Professor*  
Chizuko Toyoda, *Assistant Professor*  
Renpei Sengoku, *Assistant Professor*

Hisayoshi Oka, *Professor*  
Kazutaka Matsui, *Assistant Professor*  
Hiroshi Yaguchi, *Assistant Professor*  
Yu Kono, *Assistant Professor*

#### General Summary

Our clinical research in 2012 was conducted in the following areas: 1) neurodegenerative disease, 2) cerebrovascular disease, 3) peripheral neuropathy, 4) myasthenia gravis, and 5) migraine. We also performed basic research in the following areas: 1) neuroanatomy, 2) motoneuron disease, and 3) lipid metabolism in cerebrovascular disease.

#### Research Activities

##### *Neurodegenerative disease*

1. Evaluation of gastrointestinal function according to the Gastrointestinal Symptom Rating Scale in Parkinson's disease and the effect of nizatidine on gastrointestinal symptoms

We studied the relations of the Gastrointestinal Symptom Rating Scale scores to clinical characteristics and indices of autonomic dysfunction, such as cardiac  $^{123}\text{I}$ -metaiodobenzylguanidine uptake, heart rate variability, and orthostatic hypotension, in 28 patients with Parkinson's disease (PD). We found that patients with PD who responded to nizatidine tended to have milder cardiovascular autonomic dysfunction than did nonresponders.

2. 25-Hydroxyvitamin D, vitamin D receptor gene polymorphisms, and the severity of PD

We examined associations among serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, vitamin D receptor polymorphisms, vitamin D-binding protein gene polymorphisms, and the severity of PD. We found that higher levels of 25-hydroxyvitamin D and the vitamin D receptor FokI/CC genotype were independently associated with milder forms of PD.

3. The Odor Stick Identification Test for the Japanese can be used to differentiate PD from multiple system atrophy and progressive supranuclear palsy

We assessed olfactory function with the Odor Stick Identification Test for the Japanese (OSIT-J) in 94 Japanese patients with idiopathic PD, 15 with multiple system atrophy with predominant parkinsonism, 7 with progressive supranuclear palsy, and 29 age-matched control subjects. The OSIT-J is a potentially useful clinical test for detecting olfactory deficits in PD and for differentiating PD from progressive supranuclear palsy and multiple system atrophy with predominant parkinsonism.

4. Differences in fatigue and clinical features of the subtypes of PD

We compared the differences among fatigue and various clinical features of PD subtypes, using the 16-item Parkinson Fatigue Scale. We found that the akinetic rigid type of PD differs from the tremor-dominant type in motor impairment, fatigability, and autonomic failure.

5. Measurement of olfactory bulb volume is useful for the differential diagnosis of neurodegenerative diseases

We investigated the volume of the olfactory bulb in PD and PD-related diseases. We found that the olfactory bulb volume in patients with PD was smaller than that in patients with PD-related diseases.

6. Dysphagia and vocal cord palsy in multiple system atrophy

We assessed dysphagia and vocal cord palsy laryngoscopically in multiple system atrophy. Many patients had vocal cord palsy at the time of percutaneous endoscopic gastrostomy. We suggest that vocal cord palsy should be assessed before percutaneous endoscopic gastrostomy is performed.

7. Direct comparison of *in vivo* accumulation of 2 amyloid imaging probes, [<sup>11</sup>C] Pittsburgh compound B and [<sup>11</sup>C] BF227, in Alzheimer's disease

The purpose of this study was a direct comparison of the characteristics of 2 amyloid probes, [<sup>11</sup>C] Pittsburgh compound B and [<sup>11</sup>C]BF227, in the same patients with Alzheimer's disease. We found that the difference in the distribution of the 2 probes presumably reflects the difference in the specificity to amyloid beta or the difference in the affinity to the different stage of amyloid-beta aggregation in the senile plaque generation process or both.

8. Epidemiological study of the progression and prognosis of amyotrophic lateral sclerosis in the northern Tokatsu area of Chiba

Two medical students of The Jikei University performed epidemiological research on the progression and prognosis of ALS. They found that patients in whom lower-extremity weakness had initially developed had the slowest progression among patients with ALS, whereas patients in whom dysphagia had initially developed had rapid progression resulting in respiratory failure.

### *Cerebrovascular disease*

1. Sonothrombolysis in acute ischemic stroke

Our objective was to develop a handy transducer that can safely enhance the thrombolytic activity of recombinant tissue plasminogen activator for acute ischemic stroke. We will be creating an experimental model with bone chips to confirm the penetration of ultrasound through bone.

2. Clinical factors associated with favorable outcomes in acute ischemic stroke treated with intravenous recombinant tissue plasminogen activator

We started the Jikei Stroke Registration to investigate factors associated with favorable and poor outcomes in stroke and to compare the prognosis between stroke with in-hospital onset and stroke with out-of-hospital onset.

3. Stroke incidence in Fabry disease

We will develop a prospective registry of Fabry disease and analyze the factors associated with stroke occurrence. We will also calculate the crude incidence rate of first-ever

stroke in patients with Fabry disease.

4. Evaluation of the severity of periventricular hyperintensity using transcranial color flow imaging

We investigated the relationship between white matter lesions on magnetic resonance imaging and flow variables in the middle cerebral artery, as measured with transcranial color flow imaging. We found that the evaluation of middle cerebral artery flow variables, with the combination of the pulsatility index and end-diastolic velocity, may be useful for predicting periventricular hyperintensity.

5. Clinical characteristics associated with abnormal diffusion-weighted images in patients with transient cerebral ischemic attack

We investigated the clinical characteristics associated with diffusion-weighted image (DWI) positivity in patients with transient ischemic attack. We found that the DWI positivity rate was 35% and that the blood urea nitrogen/creatinine ratio, blood glucose level, and brain natriuretic protein level were significantly higher in DWI-positive patients than in DWI-negative patients.

6. Can eicosapentaenoic acid reduce the progression of arteriosclerosis?

We prospectively investigated whether eicosapentaenoic acid can control the progression of arteriosclerosis. At present, patients receiving eicosapentaenoic acid and a statin show a tendency for slower progression of arteriosclerosis.

*Peripheral neuropathy*

1. Neurophysiological studies of subclinical diabetic polyneuropathy

The clinical utility of nerve conduction studies and neurological examination of the feet with newly established techniques was assessed in patients with diabetes mellitus, who had neither sensory symptoms in the feet nor autonomic nervous symptoms. We found that even in patients without symptoms of neuropathy, our methods could detect subclinical peripheral or autonomic neuropathy in a certain percent of patients.

*Myasthenia gravis*

1. Administration period of tacrolimus for patients with myasthenia gravis treated with thymectomy

We have been investigating the administration period of tacrolimus for patients with myasthenia gravis treated with thymectomy.

*Migraine*

1. Beneficial effects of valproate on the floating feeling and dizziness in patients with long-standing migraine

The effects of valproate on the floating feeling and dizziness were retrospectively investigated in patients with long-standing migraine. We found that valproate was useful for treating these symptoms associated with migraine.

*Clinical researches*

1. Plasticity of glycinergic synaptic inputs in the hypoglossal nucleus

We investigated the function and development of inhibitory inputs on motoneurons to

better understand selective vulnerability. We found that glycine input increases with age and that glycine receptors ( $\alpha 3$ ) induce presynaptic plasticity.

#### 2. Study of corticospinal tract functions other than voluntary movement

We are investigating the functions of the corticospinal tract, especially sensory function, by using electrophysiological examinations. We are studying the sensory function of the corticospinal tract by using motor-evoked potentials elicited by magnetic stimulation, sensory-evoked potentials, and nerve conduction studies.

#### 3. Establishment of a high-density lipoprotein functional assay

Either bezafibrate or ethyl icosapentate was administered to patients with dyslipidemia. Cholesterol efflux was assessed using each patient's apolipoprotein B-depleted serum. We found that cholesterol efflux was significantly greater in patients receiving bezafibrate than in patients receiving icosapentate.

#### 4. Gene assay of lipid metabolism

The ATP-binding cassette transporter A1 plays a pivotal role in reverse cholesterol transport, and its degradation is inhibited by PDZRhoGEF-activate RhoA. We confirmed that PDZRhoGEF-activate RhoA knock-down with micro RNA decreases apolipoprotein A1 efflux and *in vivo* reverse cholesterol transport.

### Publications

**Kono Y, Omoto S, Sengoku R, Yaguchi H, Sonoo M, Inoue K, Mochio S.** Multifocal conduction block in a patient with sarcoid neuropathy: successful treatment with intravenous immunoglobulin. *Intern Med.* 2013; **52**: 999-1002. Epub 2012 Mar 1.

**Mitsumura H, Yogo M, Sengoku R, Furuhashi H, Mochio S.** Evaluation of very early recanalization after tPA administration monitoring by transcranial color-coded sonography. *Perspectives in Medicine.* 2012; **1**: 331-3.

**Iguchi Y, Kimura K, Sone K, Miura H, Endo H, Yamagata S, Koide H, Suzuki K, Kimura T, Sakurai M, Mishima N, Yoshii K, Fujisawa H, Ebisutani S; Kurashiki Stroke Registry investigators.** Stroke incidence and usage rate of thrombolysis in a Japanese urban city: the Kurashiki stroke registry. *J Stroke Cerebrovasc Dis.* 2013; **22**: 349-57. Epub 2011 Nov 2.

**Suzuki M, Yoshioka M, Hashimoto M, Murakami M, Noya M, Takahashi D, Urashima M.** Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. *Am J Clin Nutr.* 2013; **97**: 1004-

13. Epub 2013 Mar 13.

**Hashimoto M, Yoshioka M, Sakimoto Y, Suzuki M.** A 20-year-old female with Hirayama disease complicated with dysplasia of the cervical vertebrae and degeneration of intervertebral discs. *BMJ Case Rep.* 2012; 2012. Epub 2012 Nov 9.

**Shimoyama T, Shibasaki K, Kimura K, Uemura J, Shiromoto T, Watanabe M, Inoue T, Iguchi Y, Mochio S.** Admission hyperglycemia causes infarct volume expansion in patients with ICA or MCA occlusion: association of collateral grade on conventional angiography. *Eur J Neurol.* 2013; **20**: 109-16.

**Umehara T, Oka H, Toyoda C, Mochio S.** Pearls & Oysters: trigeminal neuropathy associated with herpes labialis. *Neurology.* 2012; **79**: e173-5.

**Shimoyama T, Iguchi Y, Kimura K, Mitsumura H, Sengoku R, Kono Y, Morita M, Mochio S.** Stroke patients with cerebral microbleeds on MRI scans have arteriolosclerosis as well as systemic atherosclerosis. *Hypertens Res.* 2012; **35**: 975-9.