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General Summary

Our clinical research in 2013 was conducted in the following areas: 1) neurodegenerative disease, 2) cerebrovascular disease, 3) peripheral neuropathy, 4) myasthenia gravis, and 5) epilepsy. We also performed basic research in the following areas: 1) induced pluripotent stem (iPS) cells and 2) lipid metabolism in cerebrovascular disease.

Research Activities

Neurodegenerative disease

1. Cardiovascular autonomic dysfunction in patients with Lewy body diseases, such as Parkinson's disease

Olfactory dysfunction in Parkinson's disease (PD) was significantly related to both cardiac sympathetic and parasympathetic dysfunction, as well as vascular sympathetic dysfunction. As nonmotor symptoms of PD, olfactory dysfunction and autonomic network failure appear to be closely related. Nizatidine was effective for improving the gastrointestinal symptoms in patients with PD of the tremor or indeterminate phenotype but not the posture and gait instability phenotype. Patients with PD for whom nizatidine was effective had milder cardiovascular autonomic dysfunction than did nonresponders.

2. A new device for long-term quantification of hypokinesia and gait bradykinesia in patients with de novo PD

We developed a new device with the MG-M1100 accelerometer (LSI Medience, Japan) to identify gait-induced accelerations based on an algorithm of pattern matching. Five healthy control subjects were asked to walk in sync with metronome beats. The gait cycle was recorded simultaneously with the accelerometer and force plates. No significant difference was observed in the gait cycle recorded with the 2 methods. Twenty-four-hour continuous recordings were obtained from 12 patients with de novo PD and 17 age-matched control subjects. In patients with PD, the number of overall movements was less than in control subjects. Several patients showed a shift of cadence to a bradykinetic rhythm and a narrow range of gait acceleration. The device also detected improvements in gait following treatment with L-DOPA. The results demonstrate that our portable gait ryhthmogram has high sensitivity for the clinically important deficits of hypokinesia and gait bradykinesia.

3. Evaluation of sialorrhea in PD with the Japanese edition of the Sialorrhea Clinical Scale for Parkinson's Disease

We administered the Japanese version of the Sialorrhea Clinical Scale for Parkinson's Disease (J-SCS-PD) questionnaire to 36 patients with PD (14 men and 22 women; mean age, 72.5 ± 8.7 years; mean disease duration, 5.9 ± 2.7 years). This questionnaire consists of 7 items: 1) diurnal sialorrhea, 2) nocturnal sialorrhea, 3) drooling severity, 4) speech impairment, 5) eating impairment, 6) frequency of drooling, and 7) social discomfort. Using the J-SCS-PD, we compared the age, disease duration, Hoehn and Yahr scale, Unified Parkinson's Disease Rating Scale, and clinical subtypes (tremor-dominant, akinetic-rigid, and mixed subtypes). The J-SCS-PD score did not differ significantly between men and women. The J-SCS-PD score correlated with age but not with disease duration or Unified Parkinson's Disease Rating Scale part III score. The mean score was significantly lower for item 5 than for the other items. Among the patients with the 3 clinical subtypes, those with the akinetic-rigid subtype had the highest J-SCS-PD score. Elderly patients had sialorrhea, but eating impairment was of less practical importance than were the other factors.

4. Dysphagia and vocal cord palsy in multiple system atrophy

Dysphagia and vocal cord palsy are not rare symptoms in advanced multiple system atrophy (MSA). Vocal cord palsy is a life-threatening risk factor at the time of percutaneous endoscopic gastrostomy (PEG). We assessed dysphagia and vocal cord palsy with laryngoscopy in cases of MSA. Many patients had vocal cord palsy at the time of PEG. In such patients, PEG should be prepared with noninvasive pressure ventilation therapy.

5. Clinical characteristics of MSA

The manifestations of MSA include movement disorder and autonomic failure. On the basis of phenotype, MSA can be divided into MSA with cerebellar features and MSA with predominant parkinsonism. We examined the clinical picture of MSA in our hospital and how it was related to the results of metaiodobenzylguanidine myocardial scintigraphy, which is an indicator of cardiac sympathetic nerve disorder. The frequency of both dysuria and orthostatic hypotension is high in MSA with cerebellar features, but the frequency of constipation was higher in MSA with predominant parkinsonism. Myocardial scintigraphy with metaiodobenzylguanidine showed denervation in about 17% of cases of MSA. These results suggested that some cases of MSA have same characteristics of Lewy body pathology.

6. Clinical features of progressive supranuclear palsy with predominant cerebellar ataxia

Progressive supranuclear palsy (PSP) is a syndrome that is typically characterized by parkinsonism, postural instability, and cognitive impairment. Our aim was to investigate the clinical characteristics of PSP with predominant cerebellar ataxia. We enrolled 4 patients. Limb and truncal ataxia, early falls, and supranuclear vertical gaze palsy without autonomic dysfunction may predict the diagnosis of PSP with predominant cerebellar ataxia.

Cerebrovascular disease

1. Sonothromolysis for hyperacute stroke with a low-frequency transducer

To increase recanalization rates and improve outcomes after ischemic stroke, ultrasound-enhanced thrombolysis (sonothrombolysis) can improve thrombolytic drug actions.

Recent results indicate that a 2-MHz transducer may be effective for clot lysis in ischemic stroke. Sonothrombolysis is a promising tool for hyperacute ischemic stroke, but its efficacy has been limited for the Asian population because of low ultrasonic penetration. Our aim is to develop a new 500-kHz transducer that improves skull penetration.

2. The effect of vertebral artery hypoplasia on posterior circulation ischemia

The purpose of this study was to evaluate the effect of vertebral artery hypoplasia on posterior circulation ischemia. Subjects were patients with acute ischemic stroke. Patients were categorized by the location of the ischemic stroke on magnetic resonance imaging (MRI).

Results: Of the 129 consecutive patients evaluated, 39 had vertebral artery hypoplasia, and 15 had vertebral artery occlusion. The prevalence of vertebral artery hypoplasia in patients with lesions in only the posterior circulation (44.4%) was significantly higher than that in patients with lesions in only the anterior circulation or with multiple lesions in both both the anterior and posterior circulations (24.7%, $p = 0.034$). Multivariate regression analysis showed that large-artery atherosclerosis, posterior circulation ischemia, and vertebral artery hypoplasia were independent factors related to vertebral artery occlusion. Vertebral artery hypoplasia was an independent factor related to vertebral artery occlusion. Therefore, vertebral artery hypoplasia likely plays a role in posterior circulation ischemia.

3. Characteristics of cerebral microbleeds in Fabry disease

Fabry disease is an X-linked inherited lysosomal storage disorder. Although white matter hyperintensity on MRI has previously been reported in patients with Fabry disease, little is known about cerebral microbleeds. Our aim was to investigate the characteristics of cerebral microbleeds in patients with Fabry disease. Of the 52 patients enrolled, 16 (31%) had cerebral microbleeds. Distinct characteristics of patients with Fabry disease and cerebral microbleeds were male sex, presence of white matter hyperintensity, and kidney dysfunction. These results may help clarify the mechanism of cerebral hemorrhage in Fabry disease.

4. The disappearance of hyperintense vessels on fluid-attenuated inversion recovery predicts a good outcome in patients treated with tissue plasminogen activator

Hyperintense vessels detected with fluid-attenuated inversion recovery MRI in patients with acute ischemic stroke indicate cerebral hypoperfusion. Thus, the disappearance of hyperintense vessels should indicate reperfusion. We investigated serial changes in hyperintense vessels in patients treated with tissue plasminogen activator (t-PA) and compared changes with clinical outcomes. A total of 118 consecutive patients were enrolled, and 52 (44%) were classified as having distal hyperintense vessels. Patients with distal hyperintense vessels had a significantly lower National Institutes of Health Stroke Scale time course ($P<0.001$) and a smaller infarct volume time course ($P<0.001$) compared with patients without distal hyperintense vessels. Multivariate analysis showed that the presence of distal hyperintense vessels was independently associated with good outcomes.

5. Intravenous recombinant t-PA injection should be prepared to treat stroke of in-hospital onset in patients with transient ischemic attack

We are uncertain of the exact clinical outcomes of stroke with in-hospital onset after the admission of patients for transient ischemic attack (TIA), especially for patients treated

with intravenous recombinant t-PA (rt-PA). The aims of our study were to investigate the frequency of TIA in patients with hyperacute stroke treated with intravenous rt-PA and to confirm that patients with TIA possess distinct embolic sources. Of the patients with acute ischemic stroke who had been treated with intravenous rt-PA, 8.5% had had TIA. Distinct embolic sources were detected in 60% of patients with TIA. This percentage was almost as high as that in patients without TIA. We suggested that TIA patients with embolic sources should be treated with rt-PA.

Peripheral neuropathy

1. Intraepidermal nerve fiber density in patients with painful neuropathy

We demonstrated the ultrastructural features of human intraepidermal nerve fibers and surrounding structures in the intercellular space with little shrinkage of keratinocytes. We also evaluated intraepidermal nerve fiber density in patients with painful neuropathy by means of confocal laser scanning microscopy and immunohistochemical staining for protein gene product 9.5.

Myasthenia gravis

1. Estimation of administration period of tacrolimus for patients with myasthenia gravis who have undergone thymectomy

We investigated the administration period of tacrolimus for patients with myasthenia gravis who have undergone thymectomy. We will perform further examinations.

Epilepsy

1. Autonomic symptoms associated with epileptic seizures

Visitor questionnaires and inpatients were investigated in regards to automatic symptoms, such as palpitations, pupillary abnormalities, respiratory changes, perspiration, a desire to urinate, and abdominal symptoms, which tend to be overlooked in the assessment of epilepsy. Common automatic disturbances were nausea and palpitations. The hypothalamic nuclei, the cerebral cortex, and the limbic system comprise a central circuit that affects the autonomic nervous system. The operculum and insular gyrus are domains apparently important for the frontal and temporal lobes since the former are accompanied by emotional change. We speculate that the frontal and temporal lobes and the limbic system are related to autonomic nervous system.

Clinical research

1. Establishment of a high-density lipoprotein functional assay

Either bezafibrate or ethyl icosapentate (EPA) were administered to patients with dyslipidemia. Cholesterol efflux was assessed in the apolipoprotein B-depleted serum of each patient. We used MRI to assess aortic plaques as a clinical outcome. Treatment with bezafibrate significantly increased serum levels of high-density lipoprotein cholesterol and apolipoprotein A-I and decreased triglyceride levels. Cholesterol efflux was greater with bezafibrate therapy than with EPA therapy, although the difference was not statistically significant. Assessment with MRI showed that bezafibrate therapy reduced aortic plaques to a greater extent than did EPA therapy, although the difference was, again, not

statistically significant.

2. Identification of high-density lipoprotein dysfunction in patients with cerebrovascular disease

Cholesterol efflux was assessed in the apolipoprotein B-depleted serum of patients with cerebrovascular disease. Other lipid profiles and the expression of genes were also analyzed. We are recruiting subjects.

3. Comparison of standard and intensive rosuvastatin therapy for 1 year with the primary outcome of aortic plaques evaluated with MRI

This study demonstrated that greater plaque regression was greater with intensive lipid-lowering with rosuvastatin than with standard therapy. We reported this result in the journal *Atherosclerosis* (2014; 232: 31-39).

4. Analysis of cerebral infarction in various types of rodents by means of a model of middle cerebral artery occlusion

In a preliminary study we created rat and mouse models of human adiponectin overexpression and a mouse model of human endothelial lipase overexpression.

5. Characteristics of α-synuclein in PD with iPS cells

Pathological accumulation of misfolded α-synuclein leading to cell dysfunction and cell death plays a central role in the pathogenesis of PD. We analyzed the α-synuclein of iPS cells generated from patients with PD. In 2013, we generated iPS cells from PD and checked how they could be differentiated to neurons by treatment with a reagent. We continue to generate iPS cells from patients with PD and to analyze them.

Publications

Kono Y, Shimoyama T, Sengoku R, Omoto S, Mitsumura H, Mochio S, Iguchi Y. Clinical characteristics associated with abnormal diffusion-weighted images in patients with transient cerebral ischemic attack. *J Stroke Cerebrovasc Dis.* 2014; **23:** 1051-5. Epub 2013 Oct 6.

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