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General Summary

Our clinical and basic research in 2019 consisted of the following topics: (1) stroke, (2) Parkinson's disease (PD), (3) neuromuscular immune-related adverse evets, and (4) amyotrophic lateral sclerosis.

Research Activities

Stroke

1. We analyzed the diagnostic ability of right-to-left shunt by transcranial color flow imaging among examiners. Because the diagnostic ability may depend on the skill of the examiner, the examination maneuvers must be standardized.
2. We investigates the difference of clinical features undergoing endovascular treatment between patients who had had an in-hospital stroke and those who had had a community-onset stroke via ambulance. Even though feasible work-flow time intervals are achieved in patients who have had an in-hospital stroke, puncture to recanalization time should be improved.
3. The NAG (initial of 3 factors, NIHSS, Anticoagulants, and Glucose) scale is a simple predictive scale for early hematoma expansion in patients with acute intracerebral hemorrhage. This study aimed to validate the usefulness of this scale at multiple institutions. In our multi-institutional validation, the NAG scale showed good discrimination.
4. We aimed to determine risk factors for lacunar infarctions and giant lacunar infarctions and to clarify who they differed in pathophysiological mechanisms. These types of infarction differed in risk factors for infarct expansion. Therefore, the underlying pathophysiological mechanisms for infarct expansion should be recognized in each type of infarction.
5. We investigated the incidence and clinical characteristics of convexity subarachnoid hemorrhage with hyperacute ischemic stroke. Hemorrhage was observed in 0.5% of patients within 4.5 hours of stroke onset and in 0.5% of patients 6 days after stroke onset.

Neurodegenerative Disease

1. Parkinson's disease

1) This study aimed to clarify whether cognitive dysfunction in PD and dementia with Lewy bodies (DLB) can be attributed to an abnormality of blood pressure. The significant association between nocturnal blood pressure dysregulation and cognitive or executive

decline in PD might be due to impaired microvascular circulation or invasion of α-synuclein in the central nervous system. The lack of a correlation of an insufficiency of blood pressure with cognitive impairment in DLB suggests initial involvement of Lewy body pathology in the neocortex, regardless of Lewy body invasion of the autonomic nervous system.

2) In this retrospective longitudinal observational study, we examined a nationwide registry data of 20,936 patients from 2008 through 2016 for patterns and trends in anti-PD drug prescriptions. These results highlight that the state of PD treatment in Japan adheres to most of the recommendations in the 2011 national guidelines but also precedes the 2018 guidelines.

3) We compared correlations of depression and anhedonia with cardiovascular sympathetic function in patients with drug-naïve PD. Depression and anhedonia might have different pathophysiological backgrounds in patients with drug-naïve PD.

4) Chronic low back pain (LBP) is a troublesome nonmotor complications of PD. This pain was present in 40.6% of patients with PD. The severity of LBP and disability in activities of daily living were associated with the severity of postural abnormality. Stooped posture was the most common cause of LBP, but 25.6% of patients had LBP that was not associated with postural abnormality.

5) This study investigated whether characteristics of white and red blood cells are associated with clinical symptoms in patients with de novo PD. Patients with normosmia, tremor-dominant or mixed type, and patients without a low body mass index have low peripheral inflammatory indices. Relative mild peripheral inflammation might play a major role in developing a mild disease phenotype in these patients.

6) We investigated the association between sympathetic nervous denervation and hemoglobin levels in patients with PD. Hemoglobin levels in these patients appear to be closely related to noradrenergic nervous activity and nigrostriatal dopaminergic degeneration.

7) We investigated the association of striatal dopaminergic depletion accompanied by sympathetic cardiovascular failure with conditions, such as orthostatic hypotension and cardiac sympathetic denervation, in patients with early PD. The presence of orthostatic hypotension and cardiac sympathetic denervation were independently associated with uptake in the putamen of ^{123}I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT).

8) A questionnaire survey was conducted of patients with PD regarding their illness, nutritional status, and dysphagia. Malnutrition in patients with PD is considered a risk of dysphagia.

9) This study compared the nuclear medicine images of patients with DLB and patients with PD and extracted findings that might help discrimination. The mean specific binding ratio and difference of the right and left sides in ^{123}I-FP-CIT single-photon emission computed tomography possibly differentiate DLB from PD.

10) In patients with untreated PD and nocturnal hypertension, the striatum uptake ratio of DaTQUANT was significantly decreased in the anterior predominance of the striatum. The reason may be that the central autonomic network containing the vagus nerve efferent nucleus has a projection path to the caudate nucleus.

2. Neuromuscular immune-related adverse events associated with immune checkpoint inhibitors
We reviewed cases of neuromuscular immune-related adverse events. They included 4 cases of myopathy and 2 cases of neuropathy. All 4 cases of myopathy presented features of both myasthenia gravis and polymyositis. Overlap of myasthenia gravis and polymyositis is apparently a feature in neuromuscular immune-related adverse events.

Basic research
1. Parkinson's disease
We analyzed human induced pluripotent stem cell (iPSC)-derived neurons from patients who have PD with the VPS35 retromer complex component gene (*VPS35*) D620N mutation and addressed relevant disease mechanisms. These results suggest that this mutation causes endosomal dysfunction in neural cells in PARK17.
2. Amyotrophic lateral sclerosis
In this study, we first made iPSCs into which mutations of 43-kDa transactivation response DNA-binding protein (TDP-43) were introduced with gene editing technology, the CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats [CRISPR]/CRISPR-associated protein 9) system. Next, we differentiated motor neurons and sensory neurons between the healthy iPSCs cells and the TDP-43 mutated iPSCs. Finally, we made models promoting progress by stress loads, such as oxidative stress.
3. Stroke
To verify a transarterial regeneration therapy, our project is aimed at developing a new focal stroke model with a microcatheter. We present a new rat model of focal stroke using a microcatheter under fluoroscopic control. The model is capable of repeated superselective administration of therapeutics directly to the cerebral artery and practicing the 3Rs principle of replacement, reduction, and refinement in experimental animals because of minimal invasiveness.

Publications

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