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General Summary

Our research in 2010 included the following: 1) an actigraphic study of tremor treated with zonisamide in patients with Parkinson's disease (PD), 2) a study of autonomic dysfunction in neurodegenerative disease, 3) neurophysiological studies of the visual information processing functions in neurodegenerative disease and of diabetic polyneuropathy, 4) neuroradiological studies with nuclear medicine, 5) ultrasonographic studies of cerebrovascular disease, and 6) basic research on motor neuron disease and axonal plasticity of the central nervous system.

Research Activities

Actigraphic study of tremor before and after treatment with zonisamide in patients with PD

Zonisamide is an antiepileptic agent that has been used to treat tremor in patients with PD in Japan since 2009 on the basis of the results of clinical and experimental studies. In this study, we used an actigraph, an instrument that can sense motion and record motor counts quantitatively, to evaluate the effectiveness of zonisamide for parkinsonian tremor. Actigraphy was performed before and after treatment with zonisamide in patients with PD. The motor count after treatment with zonisamide was significantly lower than that before treatment and objectively demonstrates that zonisamide is effective for reducing tremor in PD. We conclude that zonisamide is rapidly effective for the treatment of tremor in patients with PD.

Autonomic dysfunction in neurodegenerative disease

We studied the characteristics of subclinical autonomic nervous dysfunction in *de novo* PD without orthostatic hypotension. Autonomic nervous function, including cardiac sympathetic gain, was evaluated on the basis of cardiac radioiodinated metaiodobenzylguanidine uptake, the response to the Valsalva maneuver, and spectral analyses of the RR interval and systolic blood pressure in 20 patients who had de novo PD without orthostatic hypotension. Decreased cardiac metaiodobenzylguanidine uptake was found even in patients who had PD without orthostatic hypotension. We also observed a reduced response to the Valsalva maneuver, and performed spectral analyses of the RR interval and systolic blood pressure. These results show that latent cardiac and vasomotor sympathetic dysfunction, but not parasympathetic dysfunction, is already present in early *de novo* PD, even without orthostatic hypotension. We also studied the relation of olfactory

dysfunction to cardiovascular dysautonomia in patients with PD. We found that olfactory dysfunction in 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 in PD.

Our present study demonstrated marked impairment of olfactory sensation in Japanese patients with PD, as assessed with a simple, inexpensive, and noninvasive test, the Odor Stick Identification Test for the Japanese. This test would be useful for detecting olfactory dysfunction in PD and for differentiating PD from multiple system atrophy and progressive supranuclear palsy.

Olfactory dysfunction in Alzheimer's disease (AD) was also evaluated with a simple method using an incense stick. The subjects were 93 healthy control subjects and 16 patients with AD. The rate of olfactory dysfunction was significantly higher in patients with AD than in healthy control subjects. Furthermore, olfactory dysfunction in AD was correlated with scores on the Hasegawa Simple Intelligence Scale (revised edition).

We investigated the volume of the olfactory bulb in PD and PD-related diseases, including multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, and other neurodegenerative diseases. Olfactory bulb volume was less in patients with PD than in patients with PD-related diseases. These results are compatible with those of our postmortem study of the olfactory bulb. Magnetic resonance may be useful in the differential diagnosis of PD and PD-related diseases. We plan to perform further examinations.

Neurophysiological studies of the visual information processing functions in neurodegenerative disease and of diabetic polyneuropathy

Visual information processing functions were compared in patients with PD, dementia with Lewy bodies, and AD by means of visual and auditory event-related potentials. The findings of the study suggest that in patients with PD and dementia with Lewy bodies and visual hallucinations, but not in patients with AD, visual information processing functions are selectively impaired, compared with auditory functions.

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 no sensory symptoms in the feet, in collaboration with the Department of Diabetes, Metabolism and Endocrinology. We found that 34% of patients had subclinical polyneuropathy.

Neuroradiological studies with nuclear medicine

Neuroradiological studies were applied to neurodegenerative disorders, including dementia and parkinsonism. Brain perfusion images were compared by means of statistical imaging methods, such as 3-dimensional stereotactic surface projection analysis of iodoamphetamine single-photon emission computed tomography (SPECT) and easy Z-score imaging system analysis of 99mTc-ethyl cysteinate dimer SPECT among patients with dementia and parkinsonian disorders. These novel methods demonstrated the spectrum of pathological involvement of cholinergic and dopaminergic projections in AD and PD

and may be useful in routine clinical practice.

Ultrasonographic studies of cerebrovascular disease
Cerebrovascular ultrasonography was useful for rapidly evaluating cerebral hemodynamics in real time for patients with acute ischemic stroke. We evaluated the occlusion of intracranial arteries with transcranial color flow imaging and monitored residual flow in real time every 15 minutes for 120 minutes after bolus infusion of tissue plasminogen activator (t-PA). We were able to monitor residual flow in 4 patients who had good echo windows. Two patients had very early complete recanalization within 60 minutes after bolus infusion of the t-PA; however, occlusion persisted during the 120 minutes of monitoring in a patient with proximal occlusion of the middle cerebral artery. The National Institutes of Health Stroke Scale of 2 patients with very early recanalization was 0 at the end of treatment. Symptomatic or asymptomatic intracranial hemorrhage occurred only in patients without recanalization. Real-time ultrasound monitoring is useful for evaluating the very early thrombolytic effects of t-PA associated with early clinical recovery.

Clarifying the mechanism underlying the selective vulnerability of motoneurons
To clarify the mechanism underlying the selective vulnerability of motoneurons, we compared the membrane current responses to metabolic disturbances induced by NaCN and oxygen deprivation between neurons in the hypoglossal nucleus, the facial nucleus, the oculomotor nucleus, and the dorsal motor nucleus of the vagus nerve in brainstem slices of young rats. These results suggest that the potentiation of N-methyl-D-aspartate receptor currents through facilitated glycine release by metabolic disturbance plays a role in the link between mitochondrial dysfunction and the selective degeneration of motor neurons.

Assessment of functional recovery and axonal plasticity in paired immunoglobulin-like receptor B-deficient mice after traumatic brain injury
The myelin-associated proteins Nogo, myelin-associated glycoprotein, and oligodendrocyte myelin glycoprotein inhibit axonal plasticity. Each protein interacts with both the Nogo receptor and paired immunoglobulin-like receptor B (PirB). We examined whether blocking PirB activity enhances axonal reorganization and functional recovery after cortical injury. However, our results suggest that blocking the function of PirB is not sufficient for promoting axonal reorganization or functional recovery after cortical injury.

Publications

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