Department of Pathology
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General Summary

Our research projects have concerned neurodegenerative disorders caused by the intracellular accumulation of abnormal proteins. We are also studying mouse models of neurodegenerative disorders and autopsy cases by means of standard morphologic analysis and molecular biological analysis.

Research Activities

Logopenic primary progressive aphasia with pathologies of Alzheimer's disease and diffuse Lewy body disease

Logopenic primary progressive aphasia (lvPPA), characterized by anomia, difficulty repeating complex sentences, and phonological errors, is a group of clinically, genetically and pathologically heterogeneous disorders. The majority of lvPPA patients have underlying Alzheimer's disease with asymmetric atrophy of the language-dominant hemisphere, neurofibrillary tangles, neuritic plaques, and neuronal loss focused on the inferior frontal gyrus, motor cortex, supramarginal gyrus and superior temporal gyrus. It remains unknown whether diffuse Lewy body disease causes lvPPA or not. We report a case of Alzheimer's disease with lvPPA with asymmetric left-sided atrophy in the left inferior frontal gyrus, and temporal lobe; diffuse Lewy body disease; mild argyrophilic grain disease; cerebral amyloid angiopathy; and traumatic brain injury. Pathologies of Alzheimer's disease should primarily cause lvPPA. However, diffuse Lewy body disease with numerous Lewy bodies and Lewy neurites might evolve into disproportionately mild lvPPA and transient motor parkinsonism given the patient's pathologies of diffuse Lewy body disease.

Aggregation and phosphorylation of α-synuclein with proteinase K-resistance in focal α-synucleinopathy predominantly localized to the cardiac sympathetic nervous system

Aggregates of α-synuclein, a major component of Lewy bodies (LBs) and Lewy neurites (LNs), are distributed throughout the nervous system, including the central nervous system (CNS), sympathetic ganglia, enteric nervous system (ENS), cardiac and pelvic plexuses, submandibular gland, adrenal medulla and skin, in incidental Lewy body disease (ILBD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and pure autonomic failure (PAF). Here we report focal α-synucleinopathy predominantly localized to the cardiac sympathetic nervous system (SNS). Aggregation and phosphorylation of α-synuclein with proteinase K (PK)-resistance developed predominantly in the cytoplasm and proximal axon of the postganglionic sympathetic neuron (PGSN).

A 67-year-old man without parkinsonism or autonomic symptoms died of well-differen-

tiated squamous carcinoma of the tongue. Post-mortem brain investigation revealed neither neuronal loss nor gliosis of the substantia nigra (SN), locus coeruleus (LC), intermediate reticular zone (IRZ), nor dorsal motor nucleus of the vagus nerve (DMV). No LBs were observed in the central nervous system (CNS), including the both olfactory bulbs, nor throughout the entire spinal cord (SC). Rare LNs were found in the central gray matter (CGM) of the midbrain, IRZ of medulla oblongata, and intermediolateral nucleus (IML) of SC. Alzheimer's disease-related neuropathological changes included A0 B1 C0, without phosphorylated TDP-43 (TIP-PTD-P02) proteinopathy. Numerous intraneuritic and intracytoplasmic LBs were found in the stellate ganglia, lower cervical and upper thoracic paravertebral sympathetic trunks, and LNs in the sympathetic nerve fascicles around the aortic arch, coronary arteries, and intermyocardial vessels were immunolabeled by α-synuclein antibodies (5G4, pSyn#64, rabbit polyclonal antibodiesTP-SN-P01 and TIP-SN-P09). In PK-treated sections, immunostaining for these α-synuclein antibodies with pathologically distended structures was observed in the stellate ganglia, lower cervical and upper thoracic paravertebral sympathetic trunks, the sympathetic postganglionic fascicles around the aortic arch, extending to the epicardium, and around the intermyocardial vessels. In sections pre-treated with or without PK, a cocktail of polyclonal α-synuclein antibodies showed more peripheral and thin nerve fibers between the cardiac muscle fibers. No LBs or LNs were found in the submandibular glands, thyroid gland, bronchi, lung (trachea～bronchioles), ENS (esophagus～rectum), adrenal glands, nor abdominal para-aortic sympathetic ganglia. Given the rare LNs in the brain stem and SC, the present case was pathologically characterized as a phenotype of α-synucleinopathy predominantly localized to the cardiac SNS (from the stellate ganglia to the intermyocardial nerves). The presence of similar cases with α-synucleinopathy localized to the cardiac SNS, late-onset parkinsonism with LBs restricted to the DMV, and ILBDs with LBs and LNs predominantly localized to the adrenal gland suggests that α-synucleinopathy occurs independently as a multifocal nervous system disorder. Recently, the various α-synuclein amyloidogenic seed hypotheses were reviewed; to date, the progressive aggregation pathophysiology of α-synuclein through the formation of LBs and LNs remains unknown. The antibody against clone pSyn#64 specifically interacts with α-synuclein possessing a phosphorylated serine 129; clone 5G4 (amino acid 44-57 of α-synuclein) is specific to accumulations of misfolded and pathologically aggregated α-synuclein. Similar to amyloid-β and prion protein, PK-resistant α-synuclein accumulations play a significant role in the pathogenesis of α-synucleinopathy. The pathological findings of the present case suggest that PK-resistant α-synuclein formed throughout the entire PGSN; phosphorylation and aggregation of α-synuclein occurred at the intracytoplasmic and proximal axons of the cardiac sympathetic ganglia associated with the disturbance in axonal transport. Accumulations of cases with localized α-synucleinopathy would settle the problem of 'spreading' routes or 'seeding'. In conclusion, unusual localization of α-synucleinopathy to the cardiac SNS was observed in a patient without neurological manifestations. This focal α-synucleinopathy suggests that PK-resistant α-synuclein developed in the PGSN, where aggregation and phosphorylation of α-synuclein formed LBs and LNs in the intraganglionic cytoplasm and proximal axons. Further studies should be conducted to elucidate the progressive aggregation pathophysi-

ology of α-synuclein through the formation of LBs and LNs.

Publications

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