Department of Pathology
Division of Neuropathology

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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

Neuropathology of human immunodeficiency virus-related brain disease
Objective: This study investigated the neuropathology of human immunodeficiency virus (HIV)-related brain disease.
Material and methods: We analyzed 8 cases of HIV-related brain disease. Formalin-fixed, paraffin-embedded tissues were cut for histopathological assessment. Brain, spinal cord, and peripheral nerves were stained with hematoxylin and eosin, Krüver-Barrera, Bodian, Zeel Nielsen, Gram, periodic acid-Schiff, and Grocotte stains, and immunohistochemical examination was performed with primary antibodies against glial fibrillary acidic protein, neurofilaments, myelin basic protein, amyloid precursor protein, CD68, ionized calcium-binding adapter molecule 1, CD3, CD4, CD8, CD20, CD80, human simplex viruses 1 and 2, varicella zoster virus, human herpesvirus 6, measles, Epstein-Barr virus, histoplasma, John Cunningham virus agnoprotein, John Cunningham virus viral protein 1.
Results: We observed HIV encephalopathy in 6 cases, HIV leukoencephalopathy in 3 cases, and vacuolar myelopathy in 1 case. No cases showed neuronal loss in the cerebral cortex. Microglial activation and amyloid precursor protein-immunopositive axons were observed in 6 cases. Invasion of CD8 cells without CD4 cells was observed in the cerebral cortex in 1 case clinically diagnosed as immune reconstitution inflammatory syndrome. As HIV-related infections, progressive multifocal leukoencephalopathy, cytomegalovirus infection, Cryptococcus infection, and tuberculosis were revealed.
Discussion: From the mid-1990s, pathological findings of HIV-related brain disease changed and became complicated with the introduction of combination antiretroviral therapy. One disease is central nervous system- immune reconstitution inflammatory syndrome, defined as unexpected worsening of the neurological condition and consistent with inflammation mediated by activated CD8 T-cells. We should evaluate HIV-related brain disease with the reference of clinical information.

Autopsy of the first patient with mucopolysaccharidosis type I, Hurler-Scheie syndrome in Japan to be treated with enzyme replacement therapy
Hurler-Scheie syndrome (HSS) is a rare autosomal disorder caused by deficiency of α-L-

iduronidase, a lysosomal enzyme that hydrolyzes the terminal α-L-iduronic acid residues of dermatan sulfate and heparin sulfate. Recently, patients with HSS have effectively been treated with enzyme replacement therapy (ERT). We reported the autopsy of a 42-year-old woman with HSS who received the first treatment with ERT in Japan. The HSS had been diagnosed when the patient was 2 years old and had been treated with ERT when the patient was 30 years old. Brain weight was 875 g. Atrophy of the cerebral cortex and dilatation of the sulcus were observed. Myelopathy existed from Th4 to Th10. Ballooned neurons in the central and peripheral nervous systems were stained with Alcian blue and immunostained with antibodies against subunit c mitochondria ATP synthase. With electron microscopic examination, membranous cytoplasmic inclusions and Zebra bodies were observed in the nervous system, hepatocytes, vascular endocytes, and chondroxytes. Secondary tauopathy was observed in the limbic system and the central gray matter of the midbrain.

Administrative autopsy of a man with spinocerebellar ataxia type 31

We reported the administrative autopsy of a 64-year-old man with spinocerebellar ataxia type 31 diagnosed by histopathological findings and molecular biological analysis. Spinocerebellar ataxia type 31 is an autosomal dominant form of late-onset purely cerebellar ataxia caused by a complex pentanucleotide repeat containing $(TGGAA)_n$ in an intronic region shared by 2 genes: the brain expressed, associated with NEDD4 gene (BEAN) and the thymidine kinase 2 gene (TK2). With neuropathological examination, cerebellar Purkinje cells are preferentially affected with nuclear deformity and reduced in number and are often surrounded by halolike amorphous materials.

Publications

Wakabayashi T, Shimada Y, Akiyama K, Higuchi T, Fukuda T, Kobayashi H, Eto Y, Ida H, Ohashi T. Hematopoietic stem cell gene therapy corrects neuropathic phenotype in murine model of mucopolysaccharidosis type II. *Hum Gene Ther.* 2015; **26:** 357-66.

Hirono S, Lee EY, Kuribayashi S, Fukuda T, Saeki N, Minokoshi Y, Iwanaga T, Miki T. Importance of adult Dmbx1 in long-lasting orexigenic effect of agouti-related peptide. *Endocrinology.* 2016; **157:** 245-57.