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

The specific accumulation of subunit c of mitochondria ATP synthase and curvilinear profile in neuronal cytoplasm of methylenetetrahydrofolate reductase deficiency

Introduction: Methylenetetrahydrofolate reductase deficiency (MTHFR) is the most common inborn error of folate metabolism. Two general types of pathologic finding often have been described. In the first, intimal hyperplasia and fragmentation, subintimal fibrosis, disruption of elastic lamellae, and thromboembolism are the results of homocystinemia. In the second, neuronal loss, decreased myelination, fibrillary astrogliosis, and reduction of oligodendroglia have been attributed to decreased availability of methyl groups. We report new pathological findings; subunit c of mitochondria ATP synthase (SCMAS) accumulation and curvilinear profile (CVP) in neuronal cytoplasm of cerebral cortex.

Clinical summary: The patient was 15 year old female who originally had mental retardation (IQ 70 degree). She developed walking disturbance, psychomotor retardation, transient psychogenic blindness, tremor, and mental excitement. After she entered to hospital because of seizure during bathing, her seizure was unstable and body temperature rose to 39 degree Celsius. She suffered cardiopulmonary arrest caused by using thiopental sodium 2 mg/kg for sedation during MRI. Resuscitation was carried out but she died. FLAIR images of MRI scan showed high intensity subcortical white matter lesions located at occipital lobes. Genetic study disclosed MTHFR (compound heterozygous mutation: c.446GC>TT and c.976G>A).

Pathological findings: Postmortem examination revealed subcortical perivascular demyelination with reactive astrocytosis and infiltration of macrophages in cerebrum with SCMAS accumulation and CVP in neuronal cytoplasm of cerebral cortex.

Conclusion: The specific accumulation of SCMAS has been reported in neuronal ceroid lipofuscinosis, and other lysosomal disorders. Also in MTHFR, SCMAS accumulated and might be related to form CVP.

Accumulation of SCMAS in the central nervous system in mouse models of lysosomal diseases

Objective: This study investigated the accumulation of SCMAS in the central nervous

system in lysosomal disorders.
Material and methods: We analyzed the central nervous system of mouse models of prosaposin deficiency, GM1 gangliosidosis and mucopolysaccharidosis type II (MPS II) with biochemical methods, the amino-cupric-silver method, and immunohistochemical methods with antibodies against accumulating materials, such as SCMAS.
Results: In the central nervous system of mouse models of prosaposin deficiency, GM1 gangliosidosis and MPS II, the numbers of SCMAS-immunoreactive neurons increased in proportion to the amico-cupuric-silver-impregnated neurons.
Discussion: SCMAS is a candidate for amino-cupric-silver-impregnated material in the central nervous system of mouse models of lysosomal disorders.

Accumulation of SCMAS in the central and peripheral nervous system in human lysosomal diseases
Objective: This study investigated the accumulation of SCMAS in the central nervous system in lysosomal disorders.
Material and methods: We used SCMAS immunohistochemistry to analyze the central and peripheral nervous systems of Niemann-Pick disease type C, mucopolysaccharidoses types I, II and IV, neuronal ceroid lipofuscinoses, Gaucher disease, Fabry disease, mucolipidoses types II and III, Methylenetetrahydrofolate reductase deficiency (MTHFR). An antibody against SCMAS was raised in rabbits with keyhole limpet hemocyanin-fused DIDTAAKFIGAGAATVGVAC. An affinity-purified anti-SCMAS antibody was purified from rabbit sera with glutathione S-transferase-DIDTAAKFIGA binding column.
Results: In the central and peripheral nervous systems of lysosomal disorders, the numbers of SCMAS-immunoreactive neurons increased in proportion to the amico-cupuric-silver-impregnated neurons.
Discussion: SCMAS is reported to accumulate in the neuronal cytoplasm of neuronal ceroid lipofuscinoses and mucopolysaccharidoses types I and II. We found neuronal SCMAS accumulation in the central and peripheral nervous systems of Niemann-Pick disease type C, mucopolysaccharidoses types I and II and IV, Fabry disease, mucolipidoses, and MTHFR. The accumulation of SCMAS suggests that a disturbance of ATP synthase might cause the neuronal deaths in lysosomal disorders.

Publications

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