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Case report

An autopsy case of microencephaly, bizarre putaminal lesion, and cerebellar atrophy with heart and liver diseases

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Abstract

We reported a 64-year-old autopsy case, showing a unique combination of disorders in visceral organs and brain. She had developmental delay, microencephaly, and facial dysmorphism. She developed sick sinus syndrome and liver cirrhosis. There were no abnormalities in laboratory tests for congenital metabolic errors or anomaly syndromes, including activities of lysosomal enzymes, isoelectric focusing of serum transferrin or array comparative genomic hybridization. She died of cardiorespiratory failure. At autopsy she showed liver cirrhosis and mesangial proliferation. The brain weighed 710 g. Bizarre putaminal changes were found, in which the size of area of putamen in coronal sections was small, aberrant fiber running was increased, and immunoreactivity for tyrosine hydroxylase was reduced. Loss of Purkinje cells was found throughout the cerebellar cortex. She had unreported combination of developmental delay, facial dysmorphism, small brain, bizarre putaminal lesion, cerebellar atrophy, cardiac disease, liver cirrhosis and renal disease. Although the exact cause of disease still remains to be investigated, it will be a clue for the establishment of new disease entity to accumulate subjects having the similar phenotype.

Keywords: Facial dysmorphism; Microencephaly; Putamen; Cerebellum; Sick sinus syndrome; Liver cirrhosis

1. Introduction

Constellation of various abnormalities in the brain may coexist with structural changes in other visceral organs in anomaly syndromes, chromosomal anomalies and congenital metabolic errors such as mucopolysaccharidosis (MPS) and congenital disorders of glycosylation (CDG) [1,2]. Combined involvement of the central nervous system (CNS) and visceral organs may possibly suggest a specific pathological condition, and in order to neglect the mere coexistence, the detailed examinations, such as tests for metabolic errors, genetic analysis for anomaly syndromes and autopsy, are requiring. Recently, whole-exome sequencing in several patients has been performed to identify the causative gene for rare diseases, but that is not applicable in a single patient, unless the simultaneous analysis was done in the parent [3].

Recently we demonstrated specific immunohistochemical changes in the putamen in an autopsy case of Segawa disease, which seemed to be related to the dysfunction of the basal ganglia and the generation of levodopa-responsive dystonia [4].

Herein, we report a 64-year-old autopsy case, showing a clinico-pathological combination of cardiac disease, liver cirrhosis, microencephaly, and cerebellar

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atrophy, in addition to the fine structural changes in the putamen like those in Segawa disease.

2. Case report

The proband was born to a non-consanguineous and healthy parent at full term without asphyxia, with a birth weight of 2700 g. There was no family history of neuromuscular disorders or congenital metabolic errors. She had psychomotor retardation, and she achieved uttering words at 4 years, and independent walking at 6 years. She developed generalized tonic and clonic seizures in early infancy, lasting until the age of 60 years, regardless of anticonvulsant treatment. At 39 years, she was admitted to our center, and she showed voluntary movements in the upper extremities but not in the legs, and she was diagnosed as spastic paraplegia. She had no involuntary movements. She demonstrated microencephaly, facial dysmorphism such as coarse feature, hypertelorism, thick lip, retrognathia, and joint contractures. Chromosomal G-banding analysis was normal 46XX. There were no abnormal findings in urinary and plasma amino acid analysis, activities of lysosomal enzymes in leukocytes, organic acid profiles or isoelectric focusing of serum transferrin. At 40 years, she developed bouts of bradycardia, and she received implantation of cardiac pacemaker under the diagnosis of sick sinus syndrome. At 59 years, she was diagnosed as having liver cirrhosis, although hepatitis virus antigens and antibodies were negative. Brain magnetic resonance imaging (MRI) was not done due to the implantation of cardiac pacemaker. At 64 years, she died of heart failure subsequent to respiratory failure. Autopsy was granted by her family. Array comparative genomic hybridization (CGH) failed to show copy number variation, using autopsy liver samples. Whole-exome sequencing was not done, because the parents passed away several years before the patient's death.

At autopsy, she showed bronchopneumonia, liver cirrhosis, renal calculus and segmental mesangial proliferation. There was no steatohepatitis. The heart, including specialized cardiac muscle cells in the conducting system, had no morphological changes. The brain was small, weighing 710 g, but there seemed to be no dysplasticor destructive lesions in the surface of brain. In coronal section, the area of the cerebral hemisphere and cerebellum was small (Fig. 1), but there were no neuronal loss, ballooning of cells or gliosis in the cerebral cortex, amygdaloid body, hippocampus, or the cerebral white matter including internal capsule. The size of putamen was proportionally small. Pencil fibers in the putamen tend to run from the dorsolateral part to the ventromedial part, whereas those in the case were fragmented and seemed run randomly. We measured the area of the whole putamen (WP), and part of aberrant fiber running (PAF) in the section of right cerebrum at

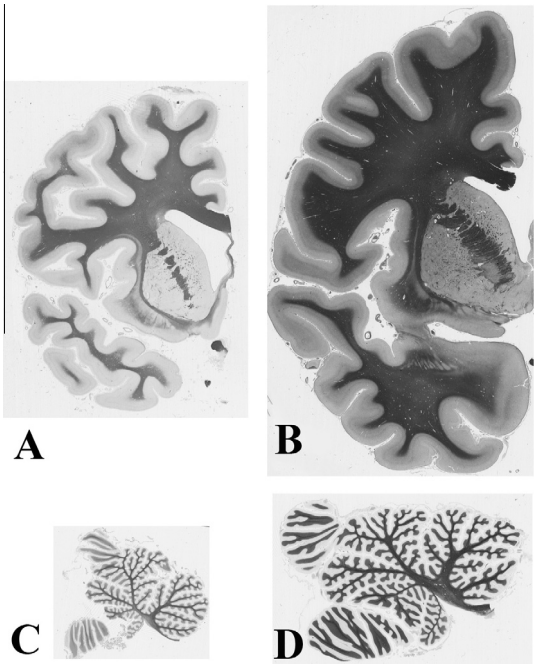

Fig. 1. Coronal section in the cerebrum and cerebellum. The area of the cerebral hemisphere was small in the case (A), being compared with that in a 69-year-old control (B). The cerebellar vermis was small in the case (C), being compared with that in a 65-year-old control (D). Klüver–Barrera staining.

the level of anterior commissure, using a Leica DMD 108 digital microimaging device (Leica Microsystems CMS GmbH, Wetzler, Germany) in our case and two controls, a 65-year-old male having oculopharyngeal muscular dystrophy and a 69-year-old female having cor pulmonale, both of which showed no changes in the brain. The WP value was 59.4 mm^2 in our case, whereas those in two controls were 113.4 and 110.0 mm^2, respectively. The PAF value was 52.7% in our case, whereas those in controls were 24.0% and 12.0%, respectively (Fig. 2A and B). In immunohistochemistry for tyrosine hydroxylase (TH) (monoclonal antibody at dilution of 1:400) (Affinity Bioreagents, CO, USA), the putamen showed reduced immunoreactivity, although that was comparatively preserved in the caudate (Fig. 2C and D). The medial and lateral segments in the globus pallidus demonstrated immunoreactivity for substance P (polyclonal antibody at dilution of 1:100) (Zymed Laboratories, Foster City, CA, USA), and methionine-enkephalin (polyclonal antibody at dilution of 1:1000) (Chemicon International, Inc., Temecula, CA, USA), respectively. Grumose foamy spheroid bodies (GFSBs) were increased in the medial segment of globus pallidus and in the substantia nigra pars reticularis (Fig. 3A). GFSB were stained by periodic acid Schiff and silver methods, and immunoreactive for ubiquitin (polyclonal antibody at dilution of 1:100) (Dako A/S, Glostrup, Denmark). There was no neuronal loss,