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Case Report

Loss of myelinated axons and astrocytosis in an autopsy case of acute encephalopathy with biphasic seizures and late reduced diffusion

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Abstract

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common pediatric encephalopathy in Japan, however, the exact neuropathology remains uncertain. The postmortem neuropathology in a patient with AESD revealed reduction of myelinated axons with early stage of astrocytosis in the absence of neuronal loss, which suggests the primary pathological damage in AESD involves myelinated axons and astrocytes rather than cortical neurons. An increased number of gemistocytic astrocytes at the corticomedullary junction may cause reduced diffusion, leading to the so-called bright tree appearance on magnetic resonance imaging, characteristic to AESD.

Keywords: Encephalopathy; Acute encephalopathy with biphasic seizures and late reduced diffusion; Brain; Pathology

1. Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common infectious pediatric encephalopathy in Japan (100–200 patients per year) [1], and is often observed in children with neurological disorders, including chromosomal abnormalities. AESD is clinically characterized by a biphasic clinical course, i.e., a prolonged febrile seizure (early seizure) on day 1, followed by a cluster of complex partial seizures (late seizures) on days 4 to 6, and is radiologically characterized by delayed reduced diffusion in the subcortical white matter, the so-called bright tree appearance (BTA), on days 3 to 9 [2,3]. Though excitotoxic injury with delayed (or apoptotic) neuronal death is hypothesized to be a possible pathomechanism based on neurochemical evaluation by magnetic resonance spectroscopy (MRS) [4,5], the exact neuropathology remains uncertain. Because of the low mortality rate for AESD (around 1%), no brain pathology is available except for one brain biopsy report on unaffected cortex [6]. We firstly report postmortem neuropathological findings of BTA in an 18 trisomy case with AESD, which revealed reduction of myelinated axons with an early stage of astrocytosis.

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2. Case report

A 1-year-old Japanese boy with trisomy 18 and cardiac anomalies (post operation for a ventricular septal defect and patent ductus arteriosus), chronic cardiac insufficiency, epilepsy (treated with phenobarbital) and horseshoe kidneys presented with a high fever of over 39.5 °C, and a cluster of complex partial seizures, lasting for several minutes on days 1 to 2. The blood and cerebrospinal fluid examinations on day 1 were almost normal, the exception being an increase of B-type natriuretic peptide (816 pg/ml, normal < 18), which was almost the same level as previously (250–800 pg/ml). Rapid antigen-detection assaying for RS virus and influenza virus was negative. On day 4, he became afebrile but his consciousness level worsened. Brain CT showed no cerebral edema or intracranial hemorrhage. Electroencephalography showed diffuse high voltage slow waves, leading to a tentative diagnosis of encephalopathy. Methylprednisolone pulse therapy (30 mg/kg × 3 days, days 4–6) was begun. Magnetic resonance imaging on day 7 revealed reduced diffusion in the white matter (high signal on diffusion-weighted images [DWI]), compatible with BTA; atrophy of the cerebrum and brain stem, and absence of a left internal carotid artery. MRS showed decreased *N*-acetyl aspartate (NAA) and increased glutamine (Gln). A biphasic clinical course, BTA on DWI, and increased Gln on MRS confirmed a diagnosis of AESD. His consciousness improved to almost the previous level on day 6, however, he presented with high fever on day 8. Urinary culture confirmed a diagnosis of upper urinary tract infection by *E. coli*. In spite of an antibiotics therapy, he continued to have high fever, and suddenly presented with bradycardia and hypotension on day 10, and died after 50 min' cardiopulmonary resuscitation. Septic shock was clinically suspected as the cause of death, which was supported by the pathological finding of shock liver.

A brain autopsy was performed ten hours after death. Informed consent was obtained from his parents. Macroscopic examination of the brain, weighing 575 g (normal for chronological age, 1050 ± 100 g), showed hypoplasia or atrophy of its entirety, including the cerebrum, cerebellum and brain stem, aplasia of the left internal carotid artery, and agenesis of the corpus callosum, but no cerebral herniation or edema. On microscopical examination, the cerebral cortex (morphology and number of neurons, and lamination), basal ganglia, thalamus, hypothalamus, optic pathways, brainstem, and cerebellum were found to be essentially preserved. The corticospinal tract in the brainstem was hypoplastic. At the corticomedullary junction of the cingulate gyrus (Fig. 1) and the frontal lobe (Fig. 2), where BTA was prominently observed on DWI, Bodian staining for axons (Fig. 1-D, 2-B), Klüver-Barrera staining for myelin and Nissl bodies in neurons (Fig. 1-E, 2-C), and the hematoxylin eosin staining (Fig. 1-C, 2-A) showed reduced staining, indicating marked reduction of myelinated axons and oligodendrocytes. Immunostaining against glial fibrillary acidic protein (GFAP) (Fig. 1-F, G, 2-D, E), a marker for astrocytes, revealed an increased number of gemistocytic astrocytes in the absence of fibrillary gliosis, suggesting an early stage of astrocytosis. Immunostaining against CD68, a marker for microglia, showed no increase in the number of microglial cells. In contrast, the occipital region with less BTA exhibited neither loss of myelinated axons in the subcortical white matter nor an increased number of astrocytes or microglial cells. The deep white matter in the cerebral cortex, including the cingulate gyrus and occipital region, showed mild fibrillary gliosis and preservation of myelinated fibers, regardless of the occurrence or not of BTA.

3. Discussion

The most important findings in this report are the reduction of myelinated axons and the increased number of gemistocytic astrocytes at the corticomedullary junction, where BTA was observed on DWI. These pathological findings are distinct from those observed in septic encephalopathy, which include diffuse blood-brain-barrier disruption and leakage, inflammatory cell migration, activation of microglia and astrocytes, and neuronal loss [7]. Brain anomalies in patients with trisomy 18 include cerebral and cerebellar hypoplasia and agenesis of the corpus callosum, which were found in the present case, and dysplasia of the hippocampus, a hypoplastic pontine nucleus, heterotopia in the cerebellar white matter, and dysplasia of the dentate nucleus [8]; however, the abnormalities observed at the corticomedullary junction have never previously been reported. In addition, these abnormalities were not observed in the unaffected occipital region, which strongly suggests that they represent the pathology of BTA.

The pathological findings are different from in the previous study of AESD, which showed activated amoeboid microglia accumulation around degenerated neurons, and astrogliosis in the cortex [6], suggesting that excessive glutamate (Glu) released from activated microglia may play an important role in the pathomechanism of AESD. However, the brain specimen was too small, comprising mostly the cortex, where no BTA was observed on DWI [6]. The present postmortem study showed neither loss of neurons nor activated microglia in the extended cortex overlying BTA, but revealed reduction of myelinated axons with an early stage of astrocytosis at the corticomedullary junction. These findings suggest that the primary pathological damage in AESD involves myelinated axons and astrocytes