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Vascular pathomechanism in 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 a childhood-onset encephalopathy, but the precise pathophysiology remains unclear. We encountered a child with Moyamoya syndrome and AESD. He exhibited left-predominant stenosis of the middle cerebral artery (MCA), and later developed broad lesions in the left hemisphere, raising the possibility that insufficient blood supply relates to formation of the lesions. To test the hypothesis, we investigated the relationship between MCA volume and lesion extent in seven AESD children without preexisting diseases. The MCA volume and lesion extent were quantified with time of flight images for construction of magnetic resonance angiography and apparent diffusion coefficient maps, respectively. Lateralization indices ([right − left]/[right + left]) of the MCA volume and lesion extent were calculated. We found that the lateralization indices were negatively correlated ($r = -0.786$, $p = .036$), that is, when the MCA volume was smaller in one side than the other side, the lesions were likely to develop more extensively in the ipsilateral side than the contralateral side. This indicates the association of insufficient blood supply with the lesions. The present study provides the first observation to suggest the involvement of vascular mechanism in AESD and has potential implications for novel therapeutic approach.

1. Introduction

Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common form of childhood-onset encephalopathy in Japan [1–3]. The first phase of AESD typically starts with a prolonged febrile seizure, followed by latent phase with variable levels of recovery in consciousness from normal to coma and no abnormalities in magnetic resonance imaging (MRI). During the period of day 4–6 of illness, patients present with a cluster of seizures and deterioration of consciousness, as the second-phase symptoms. Around this second phase (day 3–9), diffusion-weighted image (DWI) and apparent diffusion coefficient (ADC) map reveal the distinct brain lesions with reduced diffusion predominantly in the subcortical white matter. The lesions sometimes distribute entirely in the hemisphere but often spare peri-rolandic regions, named 'central sparing' [1,4]. The biphasic symptoms and abnormal imaging leads to the diagnosis of AESD.

Based on the elevated levels of glutamate in the affected regions during the latent phase on magnetic resonance spectroscopy, excitotoxic brain injury via excessive glutamate has been postulated to be pathogenetic [1,5,6]. However, the precise mechanism remains to be determined. We encountered a child with Moyamoya syndrome and

Abbreviations: ADC, apparent diffusion coefficient; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ASL, arterial spin labeling; CBF, cerebral blood flow; DCI, delayed cerebral ischemia; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; LI, lateralization index; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TOF, time of flight

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AESD, showing left-dominant stenosis of the middle cerebral artery (MCA) and broader secondary lesions in the left compared with the right sides. Based on this finding, we postulated that the insufficient blood supply could play an important role in formation of the secondary lesions. To test this hypothesis, we quantitatively examined the relationship between the size of MCA and the extent of the lesions in AESD patients without preexisting diseases.

2. Case presentation

A 9-years-old Japanese boy was brought to a hospital because of a prolonged generalized seizure with fever of 39 °C (day 1). He was born small for gestational age (2064 g for 37 weeks) and had low anorectal malformation and cholesteatoma with otitis media, which were surgically repaired. He showed short stature and had received growth hormone therapy from 7 years old. He also had mental retardation with an intelligence quotient of 40 and attended to a special school. The seizure lasted for 150 min in total until the control by intravenous administration of diazepam, midazolam and thiamylal. Magnetic resonance imaging (MRI) revealed high intensity lesions in the left corona radiata in fluid-attenuated inversion recovery (FLAIR) image. Additionally, Moyamoya syndrome was suspected in magnetic resonance angiography (MRA). The comatose status with no response to painful stimuli and the positive antigen test for influenza A virus led to the diagnosis of influenza encephalopathy. Peramivir and high-dose steroid therapy were immediately started.

On day 2 of illness, he was transferred to the intensive care unit of our hospital. He still had fever of 38.0 °C and coma with slight responses to painful stimuli (Japan coma scale of 200). MRI demonstrated hyperintensities in the left centrum semiovale in FLAIR image but no hypointensities in ADC map, indicating chronic cerebral infarction (Fig. 1a and b). MRA showed left-dominant stenosis of the supraclinoid carotid arteries and narrowing of the left MCA with collateral vessels (Fig. 1c and d), indicating Moyamoya syndrome. In addition to the previously-started therapies, therapeutic hypothermia and intraveneous immunoglobulin were immediately commenced. On day 10 of illness after the hypothermia, DWI and apparent diffusion coefficient (ADC) map revealed extensive lesions in the subcortical white matter and the basal ganglia (Fig. 1e and f), determined the final diagnosis of AESD. In the images, the cerebrum was entirely insulted in the left hemisphere but spared peri-rolandic regions in the right hemisphere, indicating 'central sparing'. He exhibited severe motor and cognitive sequelae when transferred back to the previous hospital on day 58.

3. Methods

3.1. Study population

A total of 24 AESD patients were consecutively admitted to Kyushu University Hospital during the period of 2006–2016. Among them, 20 patients were reported in our previous study [7]. We enrolled 9 patients who had time of flight (TOF) images for construction of MRA before the onset of the second phase. For six patients, the diagnosis of AESD was 'definite' according to the criteria: i) a febrile seizure as an initial neurological symptom on day 1, ii) biphasic clinical course and iii) the reduced diffusion in the subcortical white matter on day 3 or later [7]. Three patients were designated as having 'possible' AESD, because therapeutic hypothermia was started during the latent phase and thus the biphasic course was not identified. As disease controls, we also collected TOF data of 9 children with seizure disorders, which included febrile seizure and status epilepticus.

Furthermore, we examined a polymorphism of disease susceptibility gene for Moyamoya disease (c.14576G > A in *RNF213*) [8] in two other patients among the 24 AESD patients. The written informed consent was obtained from the guardians of the patients. The institutional review board of Kyushu University approved the clinical study (#28-466) and genotyping (#461-04).

3.2. Quantification of the middle cerebral arteries (MCAs)

We analyzed digital data (DICOM) of TOF images for quantification of cerebral arteries. The cerebral arteries were automatically segmented by using a 'snake evolution' method ('region competition snake') of the ITK-SNAP version 3.6.0. [9] with default values of all parameters (Fig. 2a–h). First, in the 'Presegmentation' step, we selected the 'thresholding' mode with 'lower threshold only'. The threshold of image intensities was determined for each patient in the way that the voxel intensities of the arteries were above the threshold while those of brain parenchyma were below the threshold, classified as 'background' (Fig. 2a). Second, in the 'Initialization' step, we added spherical 'bubbles', or seeds from which the 'snakes' evolve into the arteries. To lessen the load in the next step, we placed a total of 6 'bubbles' with a radius of 1 mm in the bilateral vertical portions of the internal carotid, the bilateral horizontal segments (M1) of MCA, the basilar artery and the anterior communicating artery. Third, in the 'Evolution' step, we set the 'step size' to 100 and ran the evolution until it got saturated (Fig. 2b–f). Finally, we clipped out the right and the left MCAs by using '3D scalpel tool' and measured the volumes for each MCA (Fig. 2g and h).

3.3. Quantification of lesion extents from ADC map

To quantitatively measure the extent of lesions with reduced diffusion, we analyzed DICOM of ADC maps derived from DWI with b values of 0 and 1000 s/mm^2, using 3D Slicer [10], ITK-SNAP [9] and SPM8 software, as our previous study described [7]. Briefly, the extent of lesions with reduced diffusion were quantitatively measured in the second phase (range: 3–10 days of illness, median: 5 days). Brain parenchyma was defined as the areas showing the ADC value of 1–1400 mm^2/s, and the "low ADC" was set to 1–600 mm^2/s (Fig. 2i). Meanwhile, the same parenchyma was manually segmented into the right and left MCA territories (Fig. 2j) according to a neuroanatomical atlas [11]. By using these ADC-defined and segmented data, we calculated the relative ratios of low-ADC to parenchyma volume for the two territories.

3.4. Lateralization indices (LIs) of MCA volume and lesion ratio

The obtained volumes of MCAs were derived from TOF images, which reflect cerebral blood flow (CBF). Because TOF is influenced by the settings and slice ranges of the MRI scan and patients' conditions such as consciousness state, arterial blood pressure and autonomic activity [12], the measured volumes *per se* could not be compared between patients or between different timepoints even within a patient. Thus, we calculated a lateralization index (LI) of the MCA volumes according to the following formula: LI = (Right volume − Left volume)/(Right volume + Left volume). The positive values indicate larger MCA volumes in the right than the left sides while the negative values denote the opposite. We also calculated LI of the lesion ratio in the similar manner. The positive values mean larger lesions in the right than the left sides whereas the negative values indicate the reverse. The coefficient of correlation in LI between the MCA volume and the lesion ratio was calculated using Spearman's rank correlation. Statistical analyses were performed using SPSS Statistics version 23 (IBM, Tokyo, Japan).

4. Results

4.1. Clinical expressions, MCA volume, lesion ratio and genotyping data

In a patient (Case B in Table 1), TOF images were scanned 10 months before the onset of AESD, because of his cerebral palsy, intellectual disabilities and epilepsy after severe perinatal asphyxia. This