Perfusion imaging with arterial spin labeling in acute encephalopathy with reduced subcortical diffusion following secondary generalized status epilepticus

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Key words: Acute encephalopathy; Reduced subcortical diffusion; Arterial spin labeling; Oligodendrocyte; Axonal injury

Received: May 18, 2017; Accepted: August 18, 2017

Abstract

Magnetic resonance perfusion imaging with arterial spin labeling (ASL) can provide valuable information on the circulatory changes associated with status epilepticus (SE). We report a case of a girl with an old brain abscess in the right frontal lobe who developed secondary generalized SE twice (at 3 and 4 years of age). Although she made a full recovery after the first SE, she developed acute encephalopathy with reduced subcortical diffusion (AED) following the second SE with a monophasic clinical course. We compared the ASL findings on day 4 after onset of each SE. After the first SE, ASL revealed postictal hypoperfusion in bilateral anterior circulation territories. By contrast, after the second SE, there was a marked increase in ASL signals of the entire cortex, particularly in the right fronto-parietal lobe, which corresponded to the area of reduced subcortical diffusion. Prolonged cortical hyperperfusion may have caused relative ischemia of the subcortex. As there is growing evidence that oligodendrocytes are selectively vulnerable to ischemia via glutamate-mediated excitotoxicity, our findings suggest that white matter ischemia may cause axonal injury in this case. Finding of prolonged cortical ASL hyperperfusion around day 4 after SE onset may be important for the detection of reduced subcortical diffusion.
Introduction

Assessment of cerebral perfusion using magnetic resonance imaging (MRI) techniques such as arterial spin labeling (ASL) and diffusion-weighted imaging (DWI) can provide valuable information on the metabolic and circulatory changes associated with status epilepticus (SE) [1]. During ictal periods, the epileptogenic cortex is in an electrophysiologically extreme state, with the activated cortex exhibiting increased metabolic demand, thereby causing compensatory regional hyperperfusion (termed ictal hyperperfusion) on ASL. ASL is a completely non-invasive and repeatable perfusion image technique that uses magnetically labeled blood as an endogenous tracer [1]. When this hyperperfusion is no longer sufficient to supply the hyperactive cortical area, pathophysiological changes such as uncoupling of circulation and metabolism may occur, leading to cytotoxic edema in the epileptic cortex. The affected areas appear as an abnormally high signal in the cortex (termed cortical hyperintensity) on DWI [1]. The area of cortical hyperintensity on DWI corresponds to the hyperperfused area on ASL, as the ictal hyperperfusion is a secondary change to meet the increased metabolic demand of the activated cortex [1]. The development of these MRI findings depends on the magnitude and duration of the epileptic activities, and these MRI findings are reversible in most cases [1].

By contrast, in infants with acute encephalopathy following SE, DWI may show delayed hyperintensity in the subcortical white matter rather than the cortex. This reduced subcortical diffusion is typically demonstrated in acute encephalopathy with biphasic seizures and late reduced diffusion (AED), an established encephalopathy syndrome diagnosed both by its biphasic clinical and MRI manifestations [2]. As reduced subcortical diffusion may also present in patients who are not completely compatible with the features of AED, the term acute encephalopathy with reduced subcortical diffusion (AED) was recently proposed [3, 4]. AED covers a spectrum including typical AED and atypical AED with a monophasic clinical course [4, 5], with preceding partial SE or prolonged partial epilepsy rather than febrile seizures [6], or with a predominantly unilateral hemispheric location [7].

The exact pathophysiological mechanisms of AED or AED remain unknown [2, 4]. Further, discrimination between AESD and prolonged febrile seizure in the early phase is difficult as there are no useful biomarkers [2, 4, 8]. We experienced a case of a girl with an old brain abscess in the right frontal lobe who developed secondary generalized SE twice (3 and 4 years of age). Although she made a full recovery at the first SE episode, she developed AED following the second SE with a monophasic clinical course. Herein, we compare the DWI and ASL findings on day 4 after the onset of each SE, and discuss the possible pathophysiological mechanisms of AED with respect to metabolic and circulatory changes detected on ASL and DWI.

Case Report

A Japanese girl developed pyrexia followed by generalized seizure at 1 year and 8 months of age. Based on the diagnosis of a brain abscess in the right frontal lobe, she underwent burr-hole drainage and medical treat-
ment with antibiotics. Her postoperative course was uneventful, and prophylactic anticonvulsant (200 mg per day of valproic acid (VPA) was discontinued at 3 years and 1 month of age.

However, at the age of 3 years and 10 months, she developed generalized SE and was admitted to our hospital by ambulance (day 1). On admission, she still had seizure mainly involving the left upper limb and face. Intravenous (iv) administration of diazepam terminated her seizure, and subsequent iv fosphenytoin was administered. The duration of SE was over 20 minutes. She regained consciousness the next day. On day 4, electroencephalogram (EEG) showed persistent polymorphous delta activities with interictal paroxysmal activities on the right frontal pole (Fp2 of International EEG 10-20 system) (Fig. 1A). Conventional MRI, including DWI, showed an old abscess cavity surrounded by gliosis, but failed to reveal a de novo lesion (Fig. 1B). ASL was obtained with a post-labeling delay (PLD) of 1.5 seconds, as described previously [1], using thiamylal sodium (2.2 mg/kg/dose), and revealed decreased ASL signals in the cortex of bilateral anterior circulation territories (frontal and anterior temporal lobes), but relatively increased ASL signals in the cortex of bilateral posterior circulation territories (posterior temporal and parieto-occipital lobes; posterior cortices) (Fig. 1C). The old abscess cavity had no ASL signal, while signals in the cortex of the right frontal lobe around the cavity were markedly decreased when compared with the left hemisphere. Based on a diagnosis of secondary generalized SE associated with the right frontal old lesion, 400 mg per day of VPA was re-started. The patient re-
turned home without neurological sequelae on day 5.

However, at 4 years and 6 months of age, she developed generalized SE again, and was admitted to our hospital by ambulance (day 1’ of the second SE). On admission, she still had seizure mainly involving the left upper limb and face. Intravenous diazepam terminated her seizure, and she then received iv fosphenytoin and levetiracetam (LEV). The duration of SE was over 40 minutes, although she did not regain full consciousness on day 1’. On day 2’, she partly regained consciousness, but a correct response to verbal stimuli was not obtained. EEG showed persistent polymorphous delta activities at Fp2 (Fig. 2A). Disappearance of physiological rhythmic theta activity was also noted on the right frontal region. On day 4’, she could not speak and stayed in a sitting position. EEG findings were similar to those of day 2’ and no subclinical seizure activities were noted. Although DWI did not show evidence of cortical hyperintensity (Fig. 2B), ASL demonstrated markedly increased ASL signals of the entire cortex (Fig. 2C). ASL signals of the right fronto-parietal cortex, especially around the old abscess cavity, were increased compared with the left side (Fig. 2C white solid arrows). Faint increase of ASL signals was also noted on the left frontal lobe (Fig. 2C white dashed arrow). ASL signals in bilateral posterior cortices were markedly increased compared with those observed at the first SE. A prominent increase of ASL signals was also observed in bilateral transverse sinuses, especially on the right side. Further, ASL signals of bilateral thalami and caudate heads were increased.
On day 5’, correct response to verbal stimuli was still not obtained, and the patient was irritable and grouchy. She was able to eat, and oral LEV was started, although weakness of the left upper and lower limbs became evident. On day 7’, DWI revealed a high intensity area in the subcortical white matter of the right fronto-parietal lobe, dorsal to the level of the old abscess cavity (Fig. 3A, white solid arrows). A faint hyperintense area was also noted in the left frontal subcortex (Fig. 3A, white dashed arrow). The apparent diffusion coefficient map showed low intensity in the corresponding area (Fig. 3B, white solid arrows and dashed arrow). There was a tight topographical relationship between this reduced subcortical diffusion area and the ASL hyperperfused area observed on day 4’, except for the right frontal cortex around the old abscess cavity, while there was a difference in the subcortex and cortex (Figs. 2C, 3A and B, white solid arrows and white dashed arrows).

We diagnosed her with AED, based on a monophasic clinical course following secondary generalized SE rather than prolonged febrile seizures. Steroid pulse therapy and iv edaravone and vitamin B6 were given. Follow-up MRI on day 13’ revealed disappearance of reduced subcortical diffusion, although diffuse brain atrophy was noted, especially in the right hemisphere (Fig. 3C). At 1 year of follow-up, she exhibited mental retardation (DQ68) and mild left hemiparesis, although she was free from seizures while on LEV. Follow-up MRI demonstrated marked cerebral atrophy.

Figure 3. (A) Diffusion weighted image (DWI) on day 7’ revealed a high intensity area in the subcortical white matter of the right fronto-parietal lobe, dorsal to the level of the old abscess cavity (white solid arrows). A faint hyperintensity area was also noted in the left frontal subcortex (white dashed arrow). (B) Apparent diffusion coefficient map showed a low intensity area in the same region. There was a tight topographical relationship between this reduced subcortical diffusion area and the ASL hyperperfused area observed on day 4’, although there was a difference in the cortex and subcortical white matter (white solid arrows and white dashed arrows on Figure 2C, Figure 3A and B). (C) Follow-up DWI on day 13’ showed disappearance of reduced subcortical diffusion, although diffuse brain atrophy, especially on the right side, was observed.
Discussion

Although our patient made a full recovery after the first secondary generalized SE, she developed AED following the second SE. ASL was performed on day 4 (4’) after each SE using the same dose of thiamylal sodium, when EEG showed no evidence of persistent non-convulsive SE [9]. However, on visual inspection, there was a striking difference between these ASL findings. At the first SE, ASL revealed postictal hypoperfusion in bilateral frontal and anterior temporal lobes. After the second SE, however, there was a marked increase in ASL signals in the entire cortex. Although ASL with a single PLD does not accurately reflect the cerebral blood flow (CBF) value, depending on the arterial transit time [10], increased ASL signals of the entire cortex in our case indicate prolonged hyperperfusion associated with secondary generalized SE. The most prominent hyperperfused area was located in the right frontal lobe around the old abscess cavity as the epileptogenic lesion, as we reported previously [1]. The increased ASL signals in bilateral thalami and caudates were likely a result of propagation of the epileptic activity via connections with the cortex [1]. Because of the increased venous return from both hemispheres, the arterial transit artifacts [10] of bilateral transverse sinuses, especially the right side, which result from a large amount of stagnant labeled protons in the sinuses, were strong enough to extend into the level of the parietal lobes, especially on the right side.

Interestingly, cortical hyperintensity on DWI was not demonstrated in our case, although the second SE was severe enough to induce prolonged hyperperfusion [1]. These findings indicate that neuronal injury in AED did not result from the uncoupling of circulation and metabolism of cortical neurons [2]. Cellular excitotoxicity is considered as an important pathophysiological mechanism of AESD [2, 3, 6, 11]. Indeed, MR spectroscopy revealed that glutamate was elevated in the brain during the first week in patients with AESD, while normal glutamate concentrations were found in prolonged febrile seizures [2]. Based on these findings, glutamate-mediated excitotoxic neuronal damage is likely to play an important role in the pathogenesis of AESD [2].

In our case, reduced subcortical diffusion was predominantly located in the right frontal-parietal lobe (Fig. 3A). These areas correspond well to the ASL hyperperfused area observed on day 4, although there was a difference in the subcortex and cortex (Figs. 2C, 3A and B). Using single photon emission computed tomography with $^{99m}$Tc-ethyl cysteinate dimer, Yamanouchi et al. [12] also reported increased perfusion in bilateral frontal cortices on day 4 in a patient with acute infantile encephalopathy predominantly affecting the frontal lobes. These findings suggest that the development of reduced subcortical diffusion correlates with the presence of prolonged cortical hyperperfusion. It is conceivable that prolonged cortical hyperperfusion may result in relative ischemia of the subcortex. Growing evidence also suggests that oligodendrocytes, which form a functional unit with axons and play a crucial role in axonal integrity, are selectively vulnerable to ischemia via multiple pathways such as glutamate-mediated excitotoxicity [13, 14]. Thus, glutamate excitotoxicity induced by white matter ischemia may cause...
primary axonal injury, followed by secondary neuronal injury. In support of this notion, Tanuma et al. [15] reported that cerebrospinal fluid levels of tau protein, a marker of axonal damage, were increased in patients with AESD, while neuron-specific enolase, a neuronal marker, was unchanged.

There is one other study using ASL in AESD [16], which showed that reduced ASL signals in bilateral frontal lobes on day 1 predicted the development of AESD. However, that study probably observed only postictal hypoperfusion, as seen after the first SE in our case, and did not present ASL findings around day 4 just before the appearance of reduced subcortical diffusion.

The present study has limitations. First, ischemia of the subcortical white matter could not be demonstrated on the ASL imaging, since quantitative measurements of CBF could not be achieved by the single PLD methods [10]. Furthermore, the arterial transit artifacts [10] of the cortical hyperperfusion were strong enough to extend to the level of the subcortex. Second, our experience is limited to a single AED case with a monophasic clinical course. Further studies with serial ASL examinations are required. Our findings suggest that the finding of prolonged ASL hyperperfusion around day 4 after SE may be important for the detection of AED or AESD development.

**Conflict of interest**

The authors have no financial or personal relationships that could pose a conflict of interest.

**References**


