

## Original Article

# Pseudo Continuous Arterial Spin Labeling MR Imaging of Status Epilepticus

Minkyung Yi<sup>1</sup>, Seung Hong Choi<sup>1</sup>, Keun-Hwa Jung<sup>2</sup>, Tae Jin Yoon<sup>1</sup>, Ji-Hoon Kim<sup>1</sup>, Chul-Ho Sohn<sup>1</sup>, Kee-Hyun Chang<sup>1</sup>

<sup>1</sup>Department of Radiology, Seoul National University College of Medicine, Seoul, Korea

<sup>2</sup>Department of Neurology, Seoul National University Hospital, Seoul, Korea

**Purpose :** The purpose of this study was to describe arterial spin labeling MR image findings of status epilepticus.

**Materials and Methods:** A retrospective chart review within our institute revealed six patients who had been clinically diagnosed as status epilepticus and had also undergone MR imaging that included ASL in addition to routine sequences.

**Results:** Six patients with status epilepticus were studied by conventional MR and arterial spin labeling imaging. All patients showed increased regional CBF correlating with EEG pathology. Notably, in two patients, conventional MRI and DWI showed no abnormal findings whereas pCASL demonstrated regional increased CBF in both patients.

**Conclusion:** Arterial spin labeling might offer additional diagnostic capabilities in the evaluation of patients with status epilepticus.

**Index words :** Status epilepticus · Arterial spin labeling · Cerebral blood flow · Magnetic resonance imaging (MRI)

## INTRODUCTION

Status epilepticus (SE) is a life-threatening neurologic emergency condition that requires prompt treatment. If it is not successfully treated, SE may lead to permanent pathological damage and altered physiological function of the brain resulting in significant morbidity or mortality (1–5). Traditionally, generalized convulsive status epilepticus (CSE) is defined as 30 minutes of continuous tonic-clonic seizure activity

or a series of seizures without a return to full consciousness between the seizures (6). In contrast, nonconvulsive status epilepticus (NCSE) is defined as a change in behavior or mental processes that is associated with continuous epileptiform discharges measured by electroencephalogram (EEG) in the absence of any convulsive symptoms (7). Anatomic and functional neuroimaging techniques are now standard diagnostic procedures particularly in cases such as NCSE, where clinical and EEG findings are not conclusive (8, 9).

Since epileptic activity increases metabolic demand in the local cerebral cortex, it is accompanied by temporarily increased regional brain perfusion. Measuring cerebral blood flow (CBF) and metabolic status has become a widely accepted method for localizing the zone of ictal activity (10, 11). In the same context, perfusion maps acquired using perfusion CT or perfusion MR imaging have been analyzed to identify regional hyperperfusion in SE patients (12–14).

Although there are many methods to assess CBF,

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Corresponding author : Seung Hong Choi, M.D., Ph.D., Department of Radiology, Seoul National University College of Medicine, 28, Yongon-dong, Chongno-gu, Seoul 110-744, Korea.

Tel. 82-2-2072-2861, Fax. 82-2-743-6385

E-mail : verocay@snuh.org

radioactive tracers such as <sup>99m</sup>Tc-HMPAO (hexamethyl-propylene-amine-oxime) have been traditionally used to quantify absolute CBF. Single photo emission CT (SPECT) imaging with flow-dependent radiotracers is known to aid in the diagnosis of partial SE by demonstrating increased regional CBF and metabolic activity, and this speeds the start of definitive treatment (15–17). Recent developments in MRI, however, have made non-invasive measurement of CBF possible; the emerging technique of arterial spin labeling (ASL) facilitates the noninvasive, absolute quantification of CBF without any radiation exposure to the patient and without using contrast media (18–20). Unlike nuclear medicine studies, ASL is repeatable over short time intervals. This property may lend itself to near realtime dynamic imaging of the cerebral perfusion for both ictus and interictus period (21). To our knowledge, there has been only a limited number of SE case reports assessed with ASL (21–23). We have reviewed the imaging findings of six

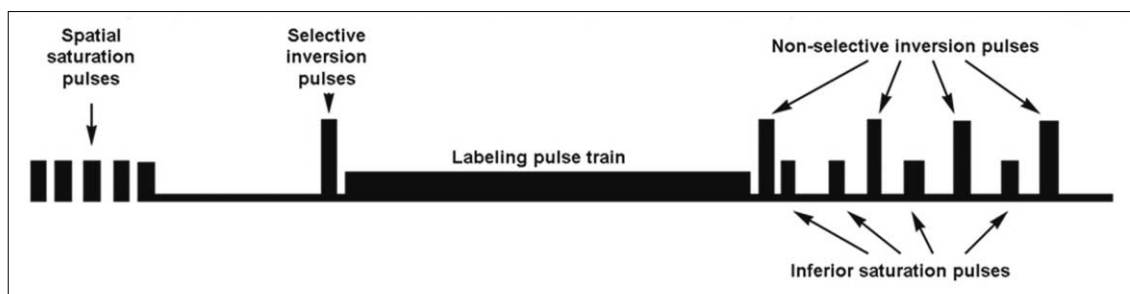
cases of SE patients who underwent ASL and investigated any additional value of applying this method towards the diagnosis of SE.

## MATERIALS AND METHODS

This retrospective study was approved by our institutional review board, and informed consent was waived.

### Study Population

A retrospective chart review within our institute revealed six patients who had been clinically diagnosed as SE and had also undergone MR imaging that included ASL in addition to routine sequences. The study took place between May 2010 and June 2011, and it included patients who presented at the emergency room with various symptoms and were diagnosed as SE based on clinical and EEG findings.



a

$$CBF = 6,000 \frac{\lambda \left( 1 - \exp\left(-\frac{2.0s}{1.2s}\right) \right) \exp\left(\frac{w(s)}{T1}\right)}{2T1(s) \left( 1 - \exp\left(-\frac{1.5}{T1(s)}\right) \right) \epsilon} \left( \frac{ASLdiff}{(45.25nex) PDref} \right)$$

b

**Fig. 1.** a. The pre and post pulses provide background suppression necessary for better contrast. Saturation was performed with crusher gradients inferior to the labeling plane, allowing for the increase in sharpness of the bolus. The arterial spin labeling experiment then consists of acquiring a labeled and a non-labeled (control) image and subtracting them to obtain the flow image. A 3D fast spin echo (FSE) spiral sequence has been implemented to acquire the signal which has prepared by the labeling sequence. The slice loop is the inner most and is acquired in a centric fashion.

b. Quantification is performed as the equation, where 1.4 s for blood at 1.5 T is assumed. The partial saturation of the ‘PD’ reference image is corrected for a T1 of 1.2 s typical of gray matter (44). While a more fully relaxed signal would be desirable, the saturation of the receiver and the bright signal on the slightly T2-weighted FSE makes this undesirable. The partition coefficient, λ, was set to the whole brain average, 0.9, and the efficiency, ε, is set to 0.80 × 0.75. This quantification assumes the label remains in blood and thus T1 of the tissue, and the delay in the arrival time to the tissue, need not be quantified.

The age of the patients (3 men and 3 women) ranged from 21 to 62 years with a mean age of 46 years at the time of diagnosis. Clinical records were reviewed to assess patient demographics, medical histories, laboratory findings, and seizure profiles.

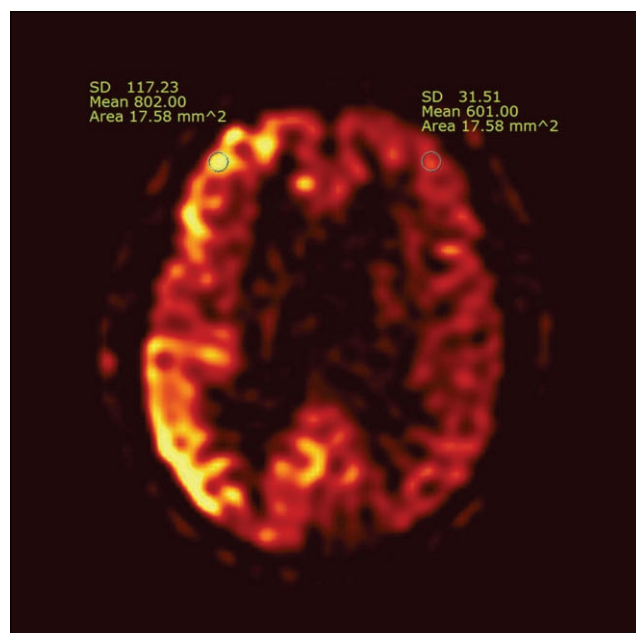
### MR imaging

MRI was performed within 1 hour after cessation of seizures in case of CSE, and after or during control of seizures in case of NCSE. All patients received proper antiepileptic medications prior to MR imaging studies. MR images were obtained using a 1.5 T MR scanner (Signa HDxt; GE Medical Systems, Milwaukee, WI) with an 8-channel head coil. The imaging protocol included an axial T2-weighted fast spin-echo sequence with the following parameters: TR/TE, 5000/131 ms; 25 sections; section thickness, 5 mm; intersection gap, 1 mm; field of view, 220 × 220 mm; matrix, 448 × 256; one acquired signal; echo train length, 16; and voxel resolution, 0.5 × 0.9 × 5.0 mm. An axial T1-weighted SE sequence was also performed as follows: TR/TE, 466/11 ms; section thickness, 5 mm; intersection gap, 1 mm; field of view, 220 × 220 mm; matrix, 320 × 192; voxel resolution, 0.7 × 1.1 × 5 mm.

Echo-planar diffusion weighted image (DWI) was performed in the axial plane, before the injection of contrast material, with the following parameters: TR/TE, 6000/63 ms; b-values, 0 and 1000 sec/mm<sup>2</sup>, 25 sections; bandwidth, 1953 Hz/voxel; section thickness, 5 mm; intersection gap, 1 mm; field of view, 240 × 240 mm; matrix, 160 × 160; two acquired signals; and voxel resolution, 1.5 × 1.5 × 5.0 mm. DWI data were acquired in three orthogonal directions and combined into a trace image. Using these data, apparent diffusion coefficient (ADC) maps were calculated on a voxel-by-voxel basis using the software incorporated within the MR imaging unit.

Recent technical advancement in the pseudo continuous ASL (pCASL) significantly increased the flow labeling efficacy within a single coil setting, which is a modification of CASL (24, 25). pCASL sequence was provided by GE Healthcare for ASL imaging (Fig. 1). Tagging is applied for 1.5 s before a postspin-labeling delay of 1.5 s. The image acquisition consisted of a stack of interleaved fast spin echo spiral readouts that each had duration of 4 ms. Each spiral arm included 512 sampling points in k-space and a total of 8 interleaves (arms) were acquired separately. In

addition, reconstruction was performed using a Fourier transform algorithm after the k-space data were regridded into 64 × 64 matrix: TR/TE, 1345/5 msec; flip angle, 155°; 32 sections; section thickness, 5 mm; no intersection gap; field of view, 240 × 240 mm; three acquired signals; echo train length, one; and voxel resolution, 3.8 × 3.8 × 5.0 mm. Background suppression, which aims to remove the signal from static tissue, was achieved using saturation pulses. Saturation was performed with crusher gradients inferior to the labeling plane, allowing for the increase in sharpness of the bolus. Image reconstruction was performed using code written in Interactive Data Language (IDL) and running on a virtual machine associated with the scanner. The images were filtered using Fermi windowing to reduce ringing artifacts. The surface coil intensity correction was not used in the present study. When the division ( $ASL_{diff}/PD_{ref}$ ) is done for CBF calculation, all the coil related shading is removed. Grad warp was not applied. After reconstruction, the images were converted into the DICOM format and inserted into the database. If at least two phases were selected, such that a reference image was available, then the difference images were converted into quantitative CBF maps.



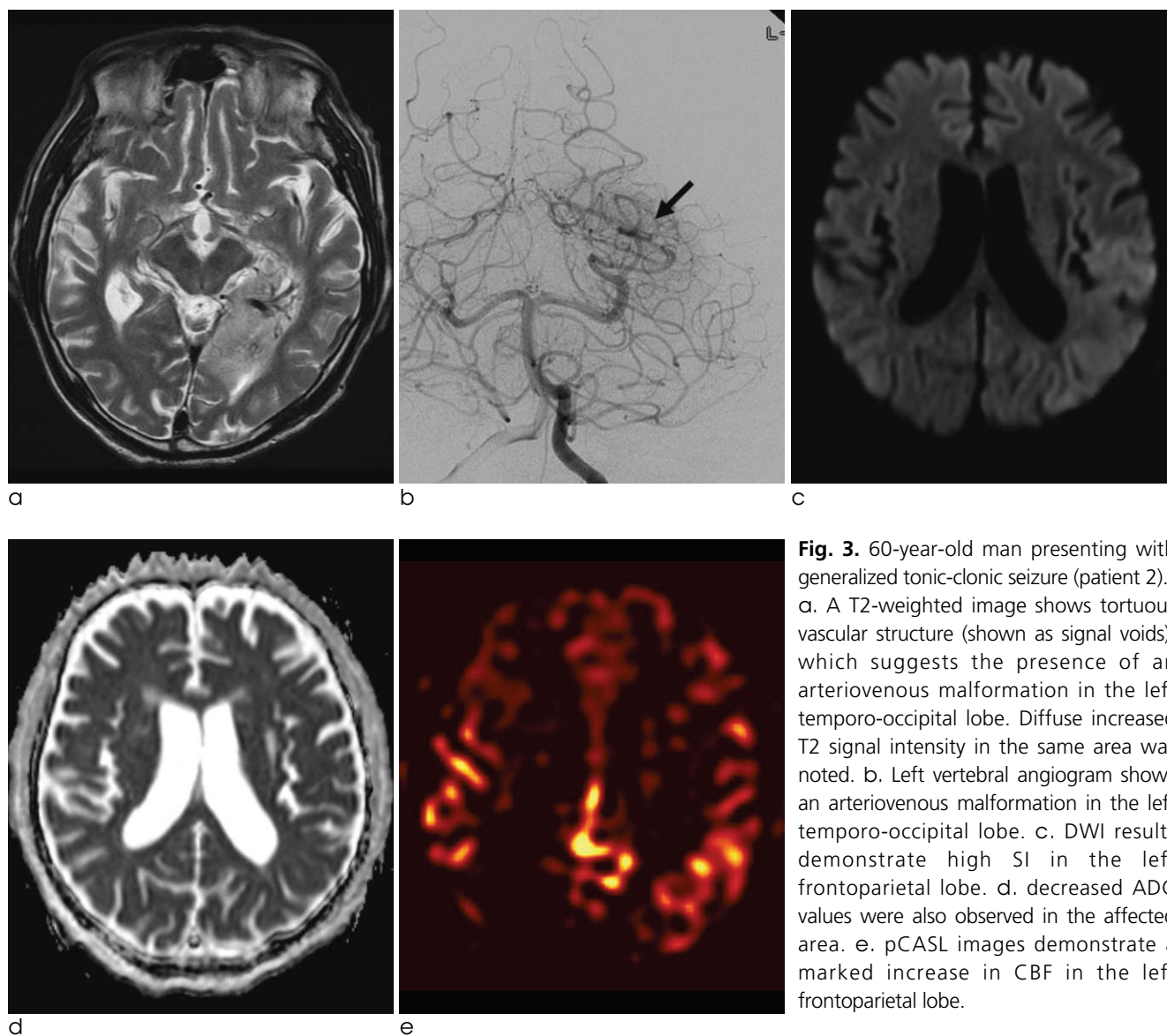
**Fig. 2.** An example of the ROI placement. ROIs were drawn in the both normal brain cortical areas and pathologic regions exhibiting the greatest CBF, and the values were recorded. CBF was calculated by dividing the measured values in ROIs by ten.

In all patients, axial T1-weighted sequences were repeated after an intravenous administration of a single dose of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma AG, Germany).

**Imaging analysis**

The images were reviewed by a neuroradiologist with 7 years of experience. Structural MR imaging data (T1-weighted and T2-weighted images) were analyzed for pre-existing abnormalities without knowledge of clinical information. DWI data were also evaluated for additional signal abnormalities, and ADC values were measured and compared with those of normal brain cortices.

In all patients, region of interests (ROIs) were drawn in the brain cortical areas exhibiting the greatest CBF, and the values were recorded (Fig. 2). This measurement was done three times for each patient, and the average value was calculated. For comparison, the CBF values within an ROI placed in the contralateral cortical region were measured and the mean value was extracted. This was not possible in patient 3: this patient exhibited bilateral regions of increased signal intensity in the parietal and occipital lobes, and reference ROI was placed randomly within normal cortical tissues.



**Fig. 3.** 60-year-old man presenting with generalized tonic-clonic seizure (patient 2). a. A T2-weighted image shows tortuous vascular structure (shown as signal voids), which suggests the presence of an arteriovenous malformation in the left temporo-occipital lobe. Diffuse increased T2 signal intensity in the same area was noted. b. Left vertebral angiogram shows an arteriovenous malformation in the left temporo-occipital lobe. c. DWI results demonstrate high SI in the left frontoparietal lobe. d. decreased ADC values were also observed in the affected area. e. pCASL images demonstrate a marked increase in CBF in the left frontoparietal lobe.

## RESULTS

Three patients presented with acute symptomatic tonic-clonic seizures; the other three patients had atypical manifestations such as headache, hallucination, or altered mentality. All cases were definitely diagnosed as CSE or NCSE by the treating medical team (26, 27). With the exception of patient 1, all EEG data were obtained during the ictal period. All EEG recordings revealed focal nonspecific or specific abnormal findings. The clinical, EEG data, and timing of ASL imaging of the patients are summarized in Table 1. The timing of ASL imaging was clinically classified as periictal or postictal according to the previous report (28).

MR images demonstrated various structural primary pathologies in two patients, whereas no specific diagnosis was made in three other patients. In patient 1, antineutrophil cytoplasmic antibody (ANCA) was positive, which suggested ANCA-associated vasculitis, while the laboratory data failed to reveal other evidence suggesting infection or metabolic abnormalities in the three other patients. Arteriovenous malformation was identified in the left medial temporo-

occipital lobe of patient 2 on angiograms (Fig. 3). Patient 5 had a history of anaplastic oligodendroglioma resection and radiotherapy in the right frontal area. All structural pathologies corresponded to abnormal lateralization and localization of EEG pathology. In patients 2 and 6, we observed increased signal intensity on DWI and decreased ADC values in the affected cortices. In contrast, patient 4 demonstrated increased signal intensity on DWI not accompanied by low ADC values, which suggests that subacute infarction had occurred. Patients 1, 3 and 5 showed no focal abnormalities on DWI or ADC maps.

Periictal or postictal pCASL perfusion MR imaging was performed for each patient within one hour following the EEG study. Patients who exhibited a structural etiology also exhibited a regional increase in CBF in the corresponding area on ASL images. Other cases without structural pathologies also demonstrated increased CBF that was localized to an area that had shown abnormal waves on EEG. The mean CBF values within ROIs located in abnormal cortex were 1.7 to 4.3 times higher than those in normal cortex.

Interestingly, in the cases of patients 1 and 3, conventional MR imaging and DWI showed no abnormal findings whereas pCASL demonstrated

**Table 1. Clinical Profiles and EEG Findings of Patients**

Patient	Age, Sex	Primary cerebral pathology	Initial presentation	Seizure Profile			Timing of ASL imaging (after cessation of seizures)
				Type	EEG (ictal or postictal)	Mental status	
1	62, M	ANCA-associated vasculitis	Headache Hallucination	NCSE	Right frontal area, slowing activity (postictal)	Confusion	Postictal (4 hours)
2	60, M	Arteriovenous malformation in the left medial temporal lobe	Generalized tonic-clonic seizure	NCSE	Left temporal area, continuous periodic lateralized epileptiform discharges (ictal)	Comatose	Periictal
3	21, F	Unknown cause	Depression, Altered mentality	NCSE	Intermittent rhythmic delta activity, bitemporal areas (ictal)	Comatose	Periictal
4	48, F	Unknown cause	Generalized tonic clonic seizure	CSE	Left temporal area, lateralized intermittent rhythmic delta activity and a few sharp waves (ictal)	Alert	Postictal (< 1 hour)
5	34, M	Anaplastic oligodendroglioma recurrence	Generalized tonic-clonic seizure	CSE	Rhythmic delta activity with evolutionary pattern in the right frontotemporal area (ictal)	Alert	Postictal (< 1 hour)
6	51, F	Unknown cause	Altered mentality, negativism	NCSE	Low amplitude rhythmic delta slowing activity in the left hemisphere (ictal)	Comatose	Periictal



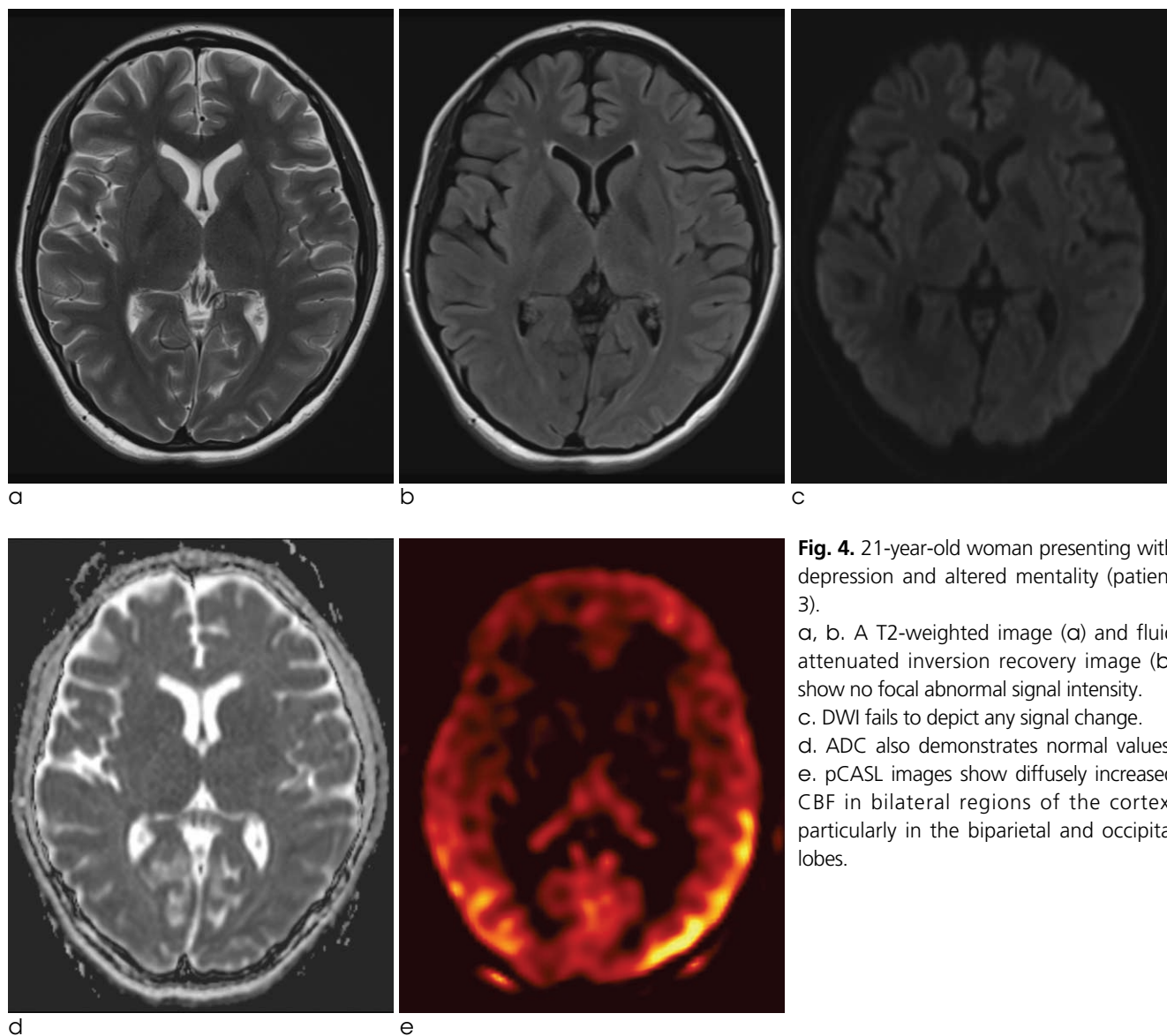
regional increased CBF in both patients; this result suggests that pCASL might offer additional diagnostic capabilities in the evaluation of patients with SE (Fig. 4). These are summarized in Table 2.

**DISCUSSION**

This study reports pCASL image findings acquired during the periictal or postictal stage of SE patients. The findings consistently demonstrate the presence, location and extent of epileptic foci in SE patients. ASL findings never contradicted the EEG findings but were the same time much better localized. The distribution of increased CBF values matched the location of

structural pathology detected on routine contrast-enhanced MR images- if such pathology was present, although the hyperemic foci on ASL imaging is not necessarily the initial focus which needs to be surgically removed (29). This result is in agreement with previous studies that showed focal increased perfusion in the epileptic foci (10-14).

ASL is a new technique that enables measurement of absolute CBF without exogenous contrast agents by using magnetically labeled water as a diffusible tracer (18, 19). Due to the increased risk of nephrogenic systemic fibrosis in conjunction with gadolinium administration, the acquisition of perfusion data in clinical populations that likely include patients with chronic renal failure patients has been problematic



**Fig. 4.** 21-year-old woman presenting with depression and altered mentality (patient 3).  
 a, b. A T2-weighted image (a) and fluid attenuated inversion recovery image (b) show no focal abnormal signal intensity.  
 c. DWI fails to depict any signal change.  
 d. ADC also demonstrates normal values.  
 e. pCASL images show diffusely increased CBF in bilateral regions of the cortex, particularly in the biparietal and occipital lobes.

**Table 2. Imaging Characteristics of Study Population**

	Location	T2	DWI / ADC	Contrast-enhanced T1	CBF (mL/100 gm/min)	CBF of normal cerebral cortices (mL/100 gm/min)
1	Right Hemisphere	Normal	Normal / Normal	Normal	146.2	34
2	Left medial temporal lobe	High signal intensity in the left medial temporal lobe including the hippocampal body and tail	High signal intensity / Decreased ADC value	Enhancement accompanied by arteriovenous malformation	233.1	76.7
3	Bilateral cortex, especially in the biparietal and occipital lobes	Normal	Normal / Normal	Normal	113.7	50
4	Left medial temporal lobe including the hippocampus and uncus	High signal intensity in the left hippocampus	Focal high signal intensity / Normal	Mild enhancement	103	36.6
5	Right frontal lobe	Gyral thickening and high T2-weighted signal intensity in the right frontal lobe	Normal / Normal	Strong enhancement	85.5	50.5
6	Left cerebral hemisphere	Gyral thickening and high T2-weighted signal intensity in the left cerebral cortex	High signal intensity / Decreased ADC values	Diffuse leptomeningeal and parenchymal enhancement	152	48

(30). ASL does not require the use of gadolinium-based contrast agents and circumvents this important issue. Another major benefit of ASL over conventional bolus techniques is that ASL can be quantitative (20). The majority of traditional perfusion techniques available are qualitative and reflect relative changes in cerebral blood volume, CBF, and mean transit time (31, 32). Quantification allows for regional and global assessments of cerebral perfusion. Relative perfusion techniques do not reveal global hypo- or hyperperfusion very easily. Quantification on an absolute scale allows easy recognition of states such as hypercapnia or diffuse hypoxic/anoxic injury. Regional assessment of cerebral perfusion allows for easy comparisons between pre- and post treatment states involving chemotherapy, endarterectomy, thrombolysis, and migraine or seizure therapy (21, 32). Interestingly, Zaharchuk et al. reported that ASL imaging revealed additional abnormalities in approximately half of patients that exhibited normal bolus perfusion weighted imaging findings. This finding suggests that ASL gives additional and complementary hemody-

amic information (33). In the present study, we used a pCASL technique to measure CBF. pCASL was introduced to match the inversion efficiency of CASL while reducing RF power deposition. First developed by Garcia et al., pCASL uses a train of discrete RF pulses in conjunction with a synchronous gradient field to mimic the flow-driven adiabatic inversion seen in CASL without the need for special hardware (25).

Kim et al. emphasized the utility of combining DWI with routine structural MR imaging in SE patients: they observed increased signal intensity on both T2-weighted and DWI images in association with diffusion restriction on ADC maps in five of enrolled eight patients, which suggests that cytotoxic edema were induced by the seizure in that area (34). In addition, Szabo et al. also reported that all patients (n=10) showed regional hyperintensity on DWI and a reduction of the ADC in their study population (14). In the present study, however, patients 1 and 3 showed no abnormal findings on routine MR sequences (including DWI) although pCASL results demonstrated abnormally increased CBF that correlated with EEG

pathology. Our results correlate well with previous reports. In the initial stage of ongoing seizure activity, abnormal electrical activity leads to a sustained twofold to threefold increase in cerebral metabolic rate of oxygen/glucose consumption (35, 36). This increase in the metabolic workload is coupled with an increase in CBF during the early phase of SE (10, 35–37). Because of this compensation, the cellular energy state can be held at close to normal values (38). Perfusion MR imaging, positron-emission tomography, and SPECT are all sensitive methods for detecting hyperperfusion at any stage (34, 39–41), but ADC fails to detect initial hyperperfusion without cell edema in this stage. Engelhorn et al. studied rats after pilocarpine-induced SE using multilocal perfusion weighted imaging for detecting the alterations of cerebral perfusion at 3, 15, 30, 60, and 120 minutes after the onset of SE (39). Transient cerebral hyperperfusion was observed immediately after SE onset for approximately 3–10 minutes, and the maximum effect was observed in the amygdala (129+/-16%) and hippocampus (130+/-21%). In addition, persistent hyperperfusion 12–24 hours after a seizure episode was reported (42), and we also observed a similar pattern in the patient 1, who showed hyperperfusion 4 hours after the cessation of seizures. Takeshita et al. reported that patients (seven of the enrolled 15 patients) with arteriovenous malformation had abnormal decreased perfusion areas in the tissues adjacent to the nidus (43); thus, we believe that hyperperfusion on ASL imaging observed in the patient 2 having arteriovenous malformation is related with SE. Finally, we believe that ASL might also have increased diagnostic value in cases of SE as a sensitive imaging modality.

Apart from the intrinsic limits of any retrospective study, several other limitations of our study should be mentioned. First, the ASL imaging was performed closely (within 1 hour) following the EEG study, but it was not simultaneous with the EEG. We interpreted the timing of the ASL study as periictal or postictal according to the EEG findings and clinical information for convenience. Second, the current study did not include a validation of ASL as a method for CBF quantification. In three patients, we observed CBF values of 34, 36.6 and 76.7 mL/100g/min in the normal cerebral cortices, which might result from quantification or measurement bias. Future study is

necessary to assess the correlation between ASL and SPECT findings in individual patients. Third, although dynamic susceptibility (DSC) imaging is widely applicable providing various parameters including CBF, MTT, TTP as well as CBV which ASL does not, the comparative standard DSC perfusion imaging data matched with ASL was not available with the patients in our study. The comparison between DSC imaging and ASL in the assessment of brain perfusion will help validation of the feasibility of ASL imaging. Fourth, we measured CBF by using subjective ROI placement on ASL imaging, which could result in the misinterpretation of CBF data of the brain. Thus, we believe that the further study using a quantitative analysis based on whole-brain voxel data from case control study is also warranted to validate our results.

## CONCLUSION

In the present study, pCASL images showed focal increased perfusion in the epileptic foci, which correlated well with EEG results. We believe that ASL is a technique that is generally recognized as safe and allows for repeated monitoring without the detriment of accumulated radiation dose or necessity of contrast infusion. However, it will be necessary to perform ASL simultaneously with SPECT or EEG monitoring for further validation of this method.

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## 간질중첩증의 동맥 스핀 라벨링 자기공명영상

<sup>1</sup>서울대학교 의과대학 영상의학교실  
<sup>2</sup>서울대학교 의과대학 서울대학교병원 신경과

이민경<sup>1</sup> · 최승홍<sup>1</sup> · 정근화<sup>2</sup> · 윤태진<sup>1</sup> · 김지훈<sup>1</sup> · 손철호<sup>1</sup> · 장기현<sup>1</sup>

**목적:** 간질중첩증의 동맥 스핀 라벨링 자기공명영상 소견을 알아보고자 한다.

**대상과 방법:** 본 기관에 내원한 환자들을 대상으로 후향적으로 검색하여 중 간질중첩증으로 임상적으로 진단받았으면서 동맥 스핀 라벨링을 포함한 자기공명영상검사를 받은 환자들을 찾아 이미지를 분석 하였다.

**결과:** 총 여섯명의 간질중첩증 환자들이 검색되었으며 이 환자들은 모두 EEG에서 이상소견이 나타난 부위에 국소적 CBF증가 소견을 보였다. 특히 두 명의 환자에서는 DWI를 포함한 고식적 자기공명영상 시퀀스에서 모두 특이 소견 보이지 않았으나 동맥 스핀 라벨링 이미지에서만 국소적으로 증가된 CBF를 보였다.

**결론:** 간질중첩증 환자들의 진단에 있어서 동맥 스핀 라벨링은 기존 영상검사에 더하여 추가적인 역할을 할 수 있을 것으로 기대된다.

통신저자 : 최승홍, (110-744) 서울시 종로구 연건동 28번지, 서울대학교 의과대학 서울대학교병원 영상의학과  
Tel. (02) 2072-2861 Fax. (02) 743-6385 E-mail: verocay@snuh.org