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Original Article

Implications and limitations of magnetic resonance perfusion imaging with 1.5-Tesla pulsed arterial spin labeling in detecting ictal hyperperfusion during non-convulsive status epileptics

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ABSTRACT

Background: Recent our reports showed that 3-T pseudocontinuous arterial spin labeling (3-T pCASL) magnetic resonance perfusion imaging with dual post labeling delay (PLD) of 1.5 and 2.5 s clearly demonstrated the hemodynamics of ictal hyperperfusion associated with non-convulsive status epilepticus (NCSE). We aimed to examine the utility of 1.5-T pulsed arterial spin labeling (1.5-T PASL), which is more widely available for daily clinical use, for detecting ictal hyperperfusion.

Methods: We retrospectively analyzed the findings of 1.5-T PASL with dual PLD of 1.5 s and 2.0 s in six patients and compared the findings with ictal electroencephalographic (EEG) findings.

Results: In patients 1 and 2, we observed the repeated occurrence of ictal discharges (RID) on EEG. In patient 1, with PLDs of 1.5 s and 2.0 s, ictal ASL hyperperfusion was observed at the site that matched the RID localization. In patient 2, the RID amplitude was extremely low, with no ictal ASL hyperperfusion. In patient 3 with lateralized periodic discharges (LPD), we observed ictal ASL hyperperfusion at the site of maximal LPD amplitude, which was apparent at a PLD of 2.0 s but not 1.5 sec. Among three patients with rhythmic delta activity (RDA) of frequencies <2.5 Hz (Patients 4–6), we observed obvious and slight increases in ASL signals in patients 4 and 5 with NCSE, respectively. However, there was no apparent change in ASL signals in patient 6 with possible NCSE.

Conclusion: The detection of ictal hyperperfusion on 1.5-T PASL might depend on the electrophysiological intensity of the epileptic ictus, which seemed to be more prominent on 1.5-T PASL than on 3-T pCASL. The 1.5-T PASL with dual PLDs showed the hemodynamics of ictal hyperperfusion in patients with RID and LPD. However, it may not be visualized in patients with extremely low amplitude RID or RDA (frequencies <2.5 Hz).

Keywords: Arterial spin labeling, Ictal hyperperfusion, Non-convulsive status epilepticus, Post labeling delay

INTRODUCTION

Arterial spin labeling (ASL) is a neuroimaging technique that noninvasively quantifies cerebral blood flow (CBF). Acting as a diffusible tracer, water proton nuclear spins in the arterial blood are labeled by the application of a radiofrequency (RF) pulse that inverts them at the level of cervical arteries.[2,3,18] A post labeling delay (PLD) is applied to facilitate the arrival of magnetically labeled blood at the region of interest, where an image is captured through magnetic resonance imaging (MRI).[2,3,18]

There are two distinct labeling methods for the clinical use of ASL,[2,5,18] namely, pulsed ASL (PASL) and pseudocontinuous ASL (pCASL). PASL involves the application of a short RF pulse to a thick (15–20 cm) "slab" area of the neck for 10–20 ms to convert the arterial water spins. Despite being an relatively easy technique, this approach has several disadvantages: lower signal-to-noise ratios (SNR); lower delivery of labeled magnetization; the visualization of intravascular ASL signals — arterial transit artifact (ATA); and greater amount of T1 decay.[2,3,18] In contrast, pCASL involves the rapid application of approximately 1000 RF pulses to the labeling plane at a goal rate of about 1/ms. This technique helps to increase the SNR, and decreases ATA and T1 decay, when compared with PASL. The 2014 consensus statement released by the International Society for Magnetic Resonance in Medicine and the European consortium ASL in Dementia recommended the use of a 3-Tesla (3-T) MRI scanner, a pCASL pulse sequence for labeling with RF pulse spacing to the shortest extent possible, the stratification of labeling duration by age, and a segmental 3D multi-echo readout.[2,18]

The use of pCASL with 3-T provides valuable information about the circulatory changes associated with non-convulsive status epilepticus (NCSE).[10, 11,13,14,16,17,19,21] During ictal periods, the epileptogenic cortex exhibits increased metabolism, thereby causing compensatory regional hyperperfusion. The "ictal hyperperfusion" is primarily detected using 3-T pCASL. When hyperperfusion is insufficient to supply the hyperactive cortical area, with the induction of glutamate excitotoxicity, pathophysiological changes can occur leading to cytotoxic edema in epileptic cortical neurons. The affected areas are secondarily detected as an abnormally high signal in the cortical lamina, designated "cortical hyperintensity" on 3-T diffusion weighted imaging (DWI). The aforementioned ictal MRI findings are reversible in most cases, but they can persist during post ictal (or peri-ictal) periods and are eventually designated as "peri-ictal MRI findings."[10,11,13,14,16,17,19,21]

However, there are very few reports on the detection of ictal ASL hyperperfusion in general clinical practices. The most likely reason is the underutilization of pCASL because of its incompatibility with MRI scanners.[2,5,18] In contrast, PASL has been available for almost two decades, and it is more widely employed because it is easier to implement.[2,5,18] Furthermore, 3-T scanning is relatively less popular than 1.5-T in local hospitals in Japan. Another possible reason is that the quantitative assessment of CBF is difficult with pCASL and completely impossible with PASL. This is because ASL is extremely sensitive to the arrival time of labeled blood in the tissue, defined as the arterial transit time.[2,3,18] The fundamental trade-off of ASL acquisition is that short PLDs do not allow the complete delivery of labeled blood to the tissue. In contrast, long PLDs result in strong T1 decay, particularly with PASL, therefore reducing the SNR. To resolve this trade-off, clinicians have traditionally used PLDs of 1.5–1.8 s.[2,3,18] However, ASL measurement with a conventional single PLD of 1.5 s leads to the underestimation of the CBF due to difficulties in assessing the slowly streaming CBF.[1,8,15,19,20]

We aimed to examine the implications and limitations of PASL imaging with 1.5-T for detecting ictal hyperperfusion during NCSE, with reference to ictal electroencephalographic (EEG) findings, which is the gold standard in NCSE diagnosis. To overcome the limitation of the inability to evaluate slowly streaming CBF, we developed a simple ASL technique using the dual PLD method. We selected another PLD of 2.5 s, in addition to the routinely used PLD of 1.5 sec.[1,8,15,19,20] We reported that 3-T pCASL with dual PLDs of 1.5 s and 2.5 s could demonstrate the hemodynamics of various pathological conditions associated with epilepsy[19] as well as steno-occlusive cerebrovascular disease,[1,7,8] dural arterio-venous fistula,[20] and giant cerebral aneurysm.[15] Herein, we selected a longer PLD of 2.0 s instead of 2.5 s to reduce the T1 shortening effect on 1.5-T PASL.

MATERIALS AND METHODS

Patients

From April 2020 to May 2021, 52 patients underwent the control of epilepsy as neuroemergency cases or postoperatively at our hospital. Most of the patients underwent neuroradiological examinations such as computed tomography or conventional MRI combined with routine EEG. In nine (17.3%) of 52 patients, PASL sequences were added to the conventional MRI examination for clinical purposes, depending on the patient's condition and at the discretion of the attending physicians.

We retrospectively selected six of these nine patients (three women and three men; mean age, 72.5 years; range, 54–81 years), who underwent both ASL and routine EEG during both ictal and interictal states of NCSE [Table 1]. The order of EEG and ASL examination varied depending on the patient. However, both were performed within a gap of several hours.

Ethics approval was obtained from the institutional review board of the Harasanshin Hospital (No. 2021-10). The need for written informed consent was waived because of the retrospective study design.

Methods

ASL imaging

MRI was performed using a 1.5-T scanner (MAGNETOM Aera; Siemens, Erlangen, Germany), equipped with a 20-channel head/neck coil. A 3-D turbo gradient spin echo and a pulsed ASL protocol were used in this study. Other acquisition parameters were as follows: phase encoding in the z direction=24, time to repeat =3000 ms, TE =17.18 ms, FOV =220 mm, matrix =64 × 52, slice thickness=3 mm, and number of slices =48. Two PLDs (inversion time) of 1500 ms (1.5 s) and 1990 ms (2.0 s) were selected. The ASL acquisition times for each PLD were 2 min and 30 s.

The evaluation of ASL findings was based on visual inspection by a board-certified radiologist (A.T.) and neurosurgeon (T.S.), blinded to the clinical data. No differences in their interpretations were observed in the independent assessments.

EEG

Routine EEG recordings were obtained using a digital EEG machine (Neurofa×1200; Nihon-Kohden, Tokyo, Japan),

Table 1: Clinical profiles, ictal EEG, and MRI findings of the patients with NCSE.

Patient No.	Age/ Sex	Symptoms	Clinical diagnosis	Epileptogenic lesion	Interval between EEG and MRI	Ictal EEG findings	Ictal MRI findings			Treatment
							ASL Localization	DWI	MRA	
1	54/F	GTCS → Impaired consciousness, Lt, hemiplegia	SFE, Subtle SE following CSE	None	EEG 1st 4 HR	RID from Rt anterior quadrant	++ Rt hemisphere	-	+	DZP, fPHT, LEV iv →propofol anesthesia →PHT, LEV po
2	82/M	Confusion	Situation related NCSE	None (Rapid correction of hyperkalemia)	EEG 1st 3 HR	RID of very low amplitude Rt occipital (O2)	-	-	-	fPHT iv
3	62/F	Aphasia	SFE, NCSE	Resected osteosarcoma, Lt temporal	EEG 1st 3 HR	LPD Lt temporal (T5)	++ Rt temporal	-	+	fPHT, LEV iv →LEV, PER po
4	79/F	GTCS → Lt hemiparesis, Eye deviation to Rt	Dementia related epilepsy, Subtle NCSE	None	MRI 1st 1 HR	1.5-Hz RDA+S Rt anterior quadrant	+ Rt frontal	-	-	fPHT iv → LEV po
5	81/M	Seizure of Lt limbs → Confusion	SFE, Subtle NCSE	After removal of Rt chronic subdural hematoma capsule	MRI 1st 4 HR	1.9-Hz RDA+S Rt anterior quadrant	+ Rt frontal	-	-	fPHT, LEV iv →LEVpo
6	77/F	Impaired consciousness	Possible NCSE	Old ICH, Lt fronto-parietal	EEG 1st 4 HR	1.5-Hz RDA+S Lt posterior quadrant	-	-	-	None

ASL: Increased signals on arterial spin labeling perfusion image, DWI: Cortical hyperintensity on diffusion weighted image, MRA: Hypervascularity on magnetic resonance angiography, F: Female, M: Male, Lt: Left, Rt: Right, GTCS: Generalized tonic clonic seizures, SFE: Symptomatic focal epilepsy, CSE: Convulsive status epilepticus, ICH: Intracerebral hemorrhage, HR: Hours, RID: Repeated occurrence of ictal discharges, LPD: Lateralized periodic discharges; RDA, Rhythmic delta activities; ++, Strongly positive; +, Mildly or slightly positive, fPHT: Fosphenytoin, LEV: Levetiracetam, PHT: Phenytoin, PER: Perampanel, iv: Intravenous administration, po: Per os

with electrode placement according to the International EEG 10–20 system. The evaluation of the EEG findings was based on visual inspection by two board-certified electroencephalographers (T.M. and H.S.) who were blinded to the clinical data. No differences in the electroencephalographers' interpretations were recorded in the independent assessments. We followed the critical care EEG terminology proposed by the American Clinical Neurophysiological Society (ACNS).[9] NCSE was diagnosed based on the Salzburg consensus criteria.[12]

RESULTS

EEG and MRI findings of the patients

In two patients (Patients 1 and 2), we observed the repeated occurrence of ictal discharges (RID) on EEG, despite an extremely low RID amplitude in patient 2. In patient 1, ictal ASL hyperperfusion was observed at the site that matched the localization of RID. However, it was not observed in patient 2. In patient 3 with lateralized periodic discharges (LPD), ictal ASL hyperperfusion was observed at the site displaying the maximal LPD amplitude. Among three patients (Patients 4–6) with rhythmic delta activity (RDA) of frequencies <2.5 Hz, we observed an obvious and slight increase in ASL signals in patients 4 and 5, respectively; in these patients, NCSE could be diagnosed with subtle ictal phenomenon. However, increased signal was not observed in patient 6 with possible NCSE. The detailed clinical, EEG, and MRI findings of these six patients are summarized in [Table 1].

Patients 1 and 2 with RID

Patient 1 developed repeated convulsive seizures due to non-lesional right frontal lobe epilepsy, predominantly in the left limbs, while changing the antiepileptic drugs. While the intravenous administration of diazepam, fosphenytoin, and levetiracetam was almost effective for convulsive seizures, her consciousness was impaired and left hemiplegia was observed. EEG showed RID, which began in the right anterior quadrant (Fp2, F4, and F8), and soon spread to the occipital (O_2) and posterior temporal regions (T6). The ictal discharges eventually became secondarily generalized [Figure 1a]. Postictal periodic discharges were observed in the right anterior quadrant. Conventional MRI, including DWI, failed to detect epileptogenic lesions or cortical hyperintensity [Figure 1b]. However, PASL images clearly detected increased signals in the right frontal, posterior temporal, and parietal lobes. At a PLD of 1.5 s, we observed the ATA of intracranial major arteries, including Willis's circle. Simultaneously, the most prominent ASL signals were observed at the interhemispheric cortex of the right frontal lobe [Figure 1c]. At a PLD of 2.0 s, the ASL signals of the right frontal interhemispheric cortex were decreased, and those of the right frontal and parietal convexities were slightly increased [Figure 1d]. ASL signals in the contralateral hemisphere were markedly decreased at PLD of 1.5 s. However, they slowly increased at PLD of 2.0 s. Time-of-flight MR angiography (MRA) showed markedly increased vascularity in the peripheries of the right middle and anterior cerebral arteries (MCA and ACA) [Figure 1e]. She was diagnosed with subtle SE, which is a persistent NCSE following convulsive seizures,[4] and general anesthesia with propofol was administered for 4 days. During interictal periods [Figure 1f], the findings of ictal hyperperfusion improved on the PASL images at PLD of 1.5 s [Figure 1g] and 2.0 s [Figure 1h] and MRA [Figure 1i].

Patient 2 developed situation-related *de novo* NCSE, possibly induced by a rapid correction of hyperkalemia (from 9.84 mmol/L to 5.61 mmol/L in approximately 5 h) with glucose-insulin therapy and hemodialysis. We repeatedly recorded ictal activities of extremely low amplitude (<20 μV) with evolving frequencies in the right occipital region on EEG, with increased sensitivity 5 times the ordinary condition, and the maximal amplitude in O_2 and P4 [Figures 2a and b]. However, the PASL image did not show ictal hyperperfusion in the right posterior cortex [Figures 2c and d]. While the ATA of the right posterior cerebral artery was noticeable, it was not estimated to increase because the signals were insignificantly different from those recorded during interictal periods [Figures 2e and f].

Patient 3 with LPD

Patient 3 underwent *en bloc* total resection of osteosarcoma of the left temporal bone.[6] Despite an uneventful postoperative course, she suddenly developed aphasia on the third postoperative month. EEG revealed LPD with the maximal amplitude in the posterior temporal region of T5 [Figure 3a]. Conventional MRI showed a surgical defect in the left temporal lobe, with an enlargement of the inferior horn. Nonetheless, there was no tumor recurrence [Figure 3b]. A PLD of 1.8 s was added between the dual PLDs. At a PLD of 1.5 s, with prominent ATA of major arteries, particularly the left MCA, we observed decreased signals of the left posterior temporal lobe and the postero-dorsal part of the resection cavity [Figure 3c]. At PLDs of 1.8 s and 2.0 s, the ASL signals of the left posterior temporal lobe gradually increased. In contrast, ATA of the major arteries decreased [Figures 3d and e]. MRA revealed hypervascularity in the periphery of the MCA [Figure 3f]. Following NCSE diagnosis, the patient was orally administered levetiracetam and perampanel, following intravenous fosphenytoin and levetiracetam, and her aphasia disappeared. During interictal periods, increased ASL signals of the left posterior temporal lobe were improved. EEG showed persistent polymorphous delta activity with sporadic paroxysmal activities in the left posterior temporal region.

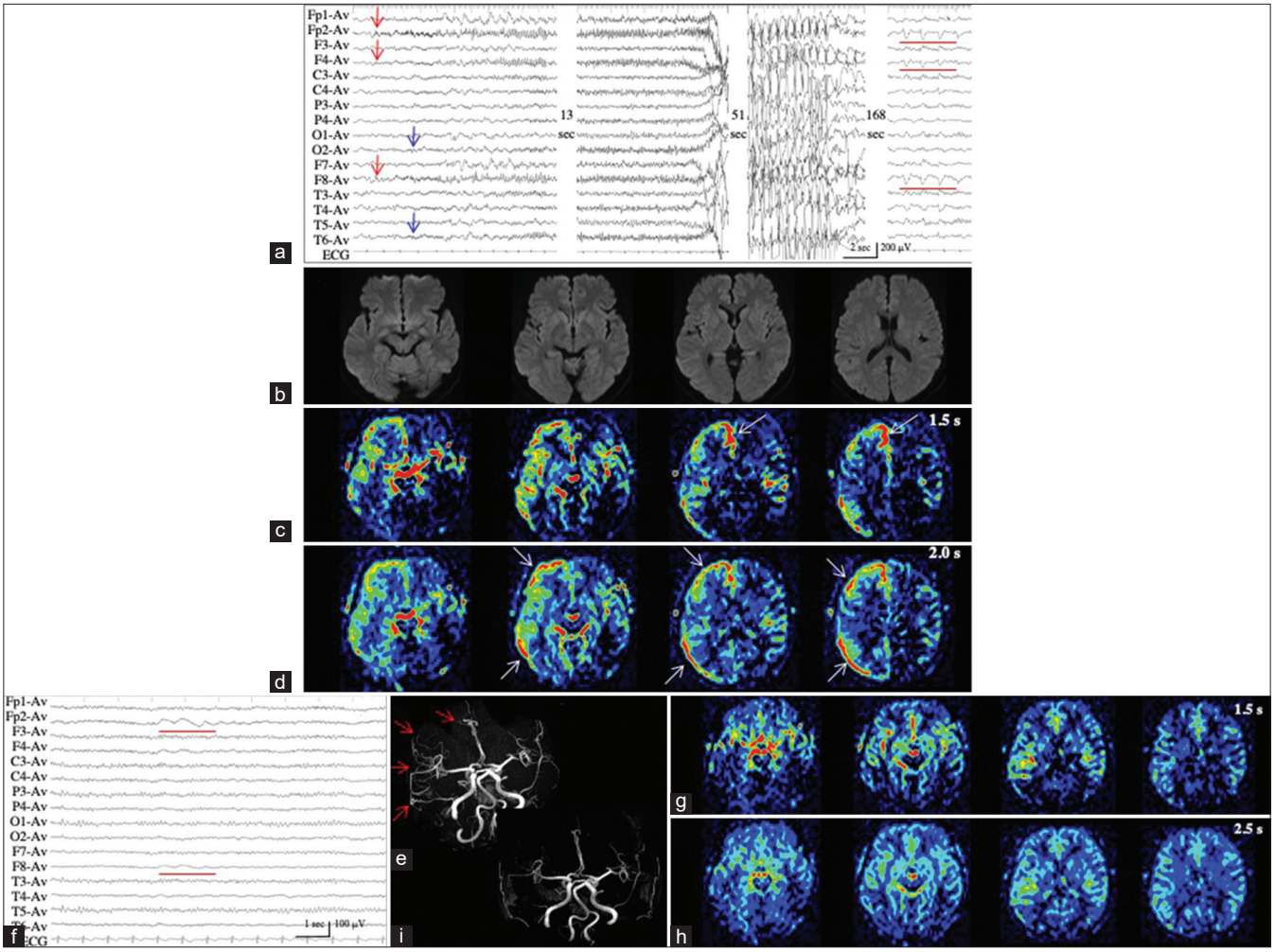

Figure 1: Patient 1. (a) EEG during ictal periods shows that ictal discharges begin at the right anterior quadrant (red arrows, Fp2, F3, and F8 of International EEG 10–20 system), soon spread to the occipital (O_2) and posterior temporal regions (T6) (blue arrows), and eventually become secondarily generalized. Postictally, periodic discharges are observed at the right anterior quadrant (red lines). (b) Diffusion weighted images fail to reveal an epileptogenic lesion or cortical hyperintensity. (c and d) PASL images with PLD of 1.5 s (c) and 2.0 s (d) reveal increased signals in the right frontal, posterior temporal, and parietal lobes. At PLD of 1.5 s, the ATA of intracranial major arteries, including Willis's circle, is observed. The most prominent ASL signals are observed at the interhemispheric cortex of the right frontal lobe (white arrows in (c)). At PLD of 2.0 s, while ASL signals of the right frontal interhemispheric cortex are slightly decreased, those of right frontal, posterior temporal, and parietal convexity are slightly increased (white arrows in (d)). (e) Time-of-flight MRA shows increased vascularity at the peripheries of MCA and ACA (red arrows). (f) During interictal periods (2 weeks after (a)), EEG reveals intermittent slow wave activities in the right frontal region (red lines: Fp2, F4, and F8). The background activities of the right hemisphere are decreased. (g and h) Both on PASL with PLD of 1.5 s (g) and 2.0 s (h), the findings of ictal ASL hyperperfusion are improved. (i) MRA shows no increased vascularity at the peripheries of right MCA and ACA. EEG: Electroencephalogram, AV: Averaged reference, PASL: Pulsed arterial spin labeling, PLD: Post labeling delay, ATA: Arterial transit artifact, ASL: Arterial spin labeling, MRA: Magnetic resonance angiography, MCA: Middle cerebral artery, ACA: Anterior cerebral artery.

Patients 4–6 with RDA

Patient 4 had moderate dementia, developed generalized tonic-clonic seizures at the nursing home, and were admitted to our hospital. On arrival, while the seizure subsided, her consciousness was impaired. Moreover, we observed left hemiparesis and eye deviation to the right. EEG revealed 1.5-Hz RDA with sharp waves in the right anterior quadrant [Figure 4a]. Conventional MRI failed to reveal the epileptogenic region. However, PASL at a PLD of 2.0 s showed an obvious increase in ASL signals in the right frontal and temporal lobes [Figure 4b]. ASL signals on the contralateral side had decreased. On MRA, hypervascularity was not apparent at the periphery of the right MCA [Figure 4c]. Despite diagnosing possible NCSE only from the EEG findings, she was diagnosed with subtle SE, based

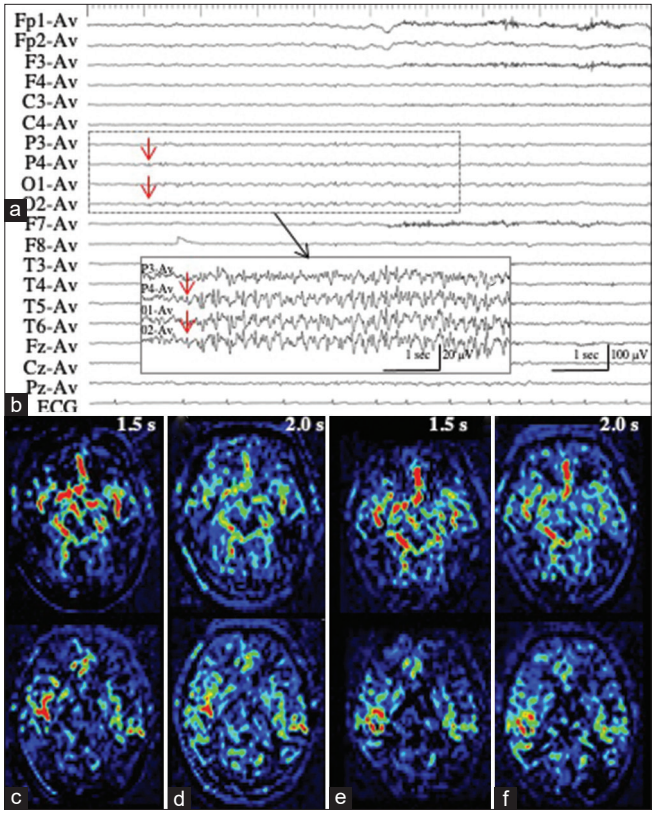

Figure 2: Patient 2. (a, black arrow) During ictal periods, EEG shows ictal discharges of extremely low amplitude (<20 μV) in the right occipital region (red arrows). (b) EEG with increased sensitivity 5 times the ordinary condition clearly shows repeated occurrence of ictal discharges with evolving frequencies, with the maximal amplitude in 02 and P4 (red arrows). The area of EEG with increased sensitivity is indicated by the dotted square in (a, black arrow). (c and d) PASL images with PLD of 1.5 s (c) and 2.0 s (d) fail to reveal the ictal hyperperfusion in the right posterior cortex. (e and f) During interictal periods, PASL images with PLD of 1.5 s (e) and 2.0 s (f) show similar findings with those of ictal PASL. The ATA of the right posterior cerebral artery is slightly noticeable both on ictal (c and d) and interictal PASL images (e and f). EEG: Electroencephalogram, PASL: Pulsed arterial spin labeling, PLD: Post labeling delay, ATA: Arterial transit artifact.

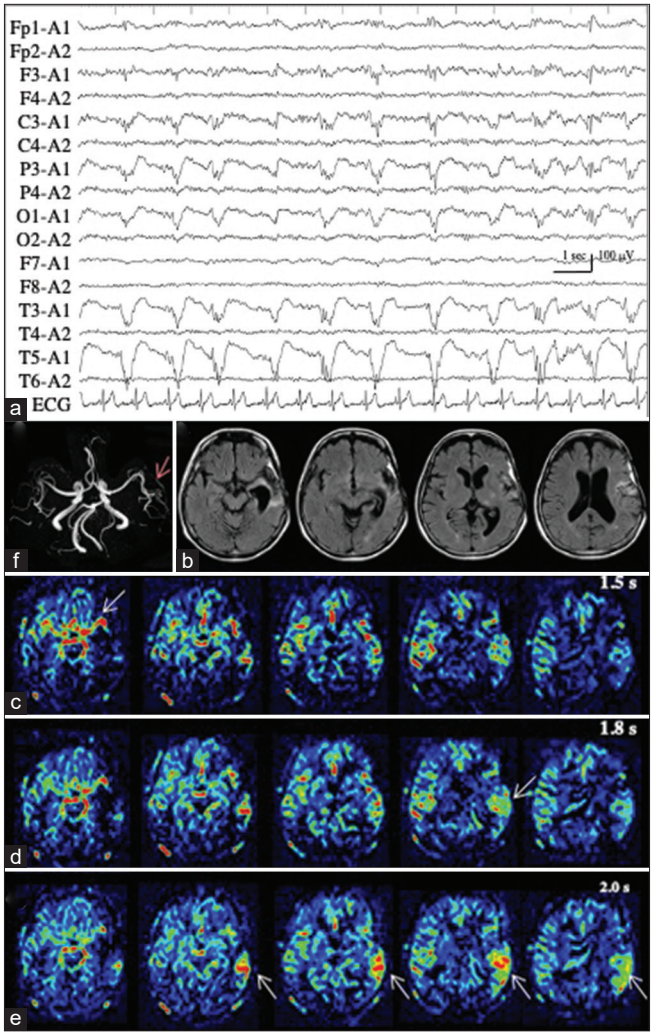

Figure 3: Patient 3. (a) Ictal EEG shows LPD with the maximal amplitude on the posterior temporal region of T5. (b) MR images with fluid attenuated inversion recovery sequence show a surgical defect in the left temporal lobe, with enlargement of the inferior horn. (c-e) PASL images with PLD of 1.5 s (c), 1.8 s (d), and 2.0 s (e) clearly show the hemodynamics of ictal hyperperfusion. At PLD of 1.5 sec, when the ATA of major arteries, particularly left MCA, is prominent (white arrow in (c)), increased ASL signals of the left posterior temporal lobe, the postero-dorsal part of the resection cavity, is not apparent. The ASL signal of the left posterior temporal lobe is slightly increased at PLD of 1.8 s (white arrow in (d)), and apparently increased at PLD of 2.0 s (white arrows in (e)). ATA of major arteries is decreased. (f) MRA reveals the hypervascularity at the periphery of left MCA (red arrow). EEG: Electroencephalogram, LPD: Lateralized periodic discharges, MR: Magnetic resonance, PASL: Pulsed arterial spin labeling, PLD: Post labeling delay, MCA: Middle cerebral artery, ASL: Arterial spin labeling, ATA: Arterial transit artifact, MRA: Magnetic resonance angiography.

on the subtle ictal findings, including eye deviation. Oral levetiracetam was administered following intravenous fosphenytoin. During the interictal period, the laterality of the ASL signals disappeared [Figure 4d].

Patient 5 underwent right fronto-temporo-parietal craniotomy for the removal of the recurrent chronic subdural hematoma capsule. On postoperative day 2, he developed clonic seizures in his left limbs, followed by a state of confusion. EEG showed a 1.9-Hz RDA with sharp waves in the right anterior quadrant [Figure 5a]. On DWI, the deviation of the right cerebral hemisphere was persistent. However, there was no parenchymal change [Figure 5b]. On ASL at PLD of 1.5 s, we observed a slightly increased area in the right frontal lobe [Figure 5c], which was not apparent at PLD of 2.0 s [Figure 5d]. Possible

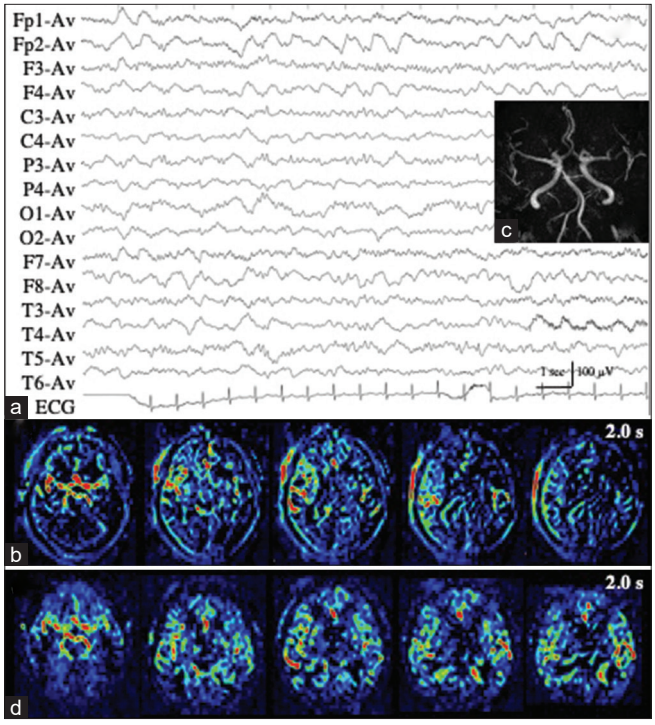

Figure 4: Patient 4. (a) Ictal EEG reveals 1.5-Hz RDA with sharp waves in the right anterior quadrant. (b) PASL at PLD of 2.0 s shows obviously increased ASL signals in the right frontal lobe. ASL signals of the contralateral hemisphere are decreased. (c) On MRA, the hypervascularity is not apparent at the periphery of the right middle cerebral arteries. (d) On interictal PASL at PLD of 2.0 sec, the increased ASL signals are improved. PASL images at PLD of 1.5 s are not available because of technical failures, both on the ictal and interictal periods. EEG: Electroencephalogram, RDA: Rhythmic delta activities, PASL: Pulsed arterial spin labeling, PLD: Post labeling delay, MRA: Magnetic resonance angiography.

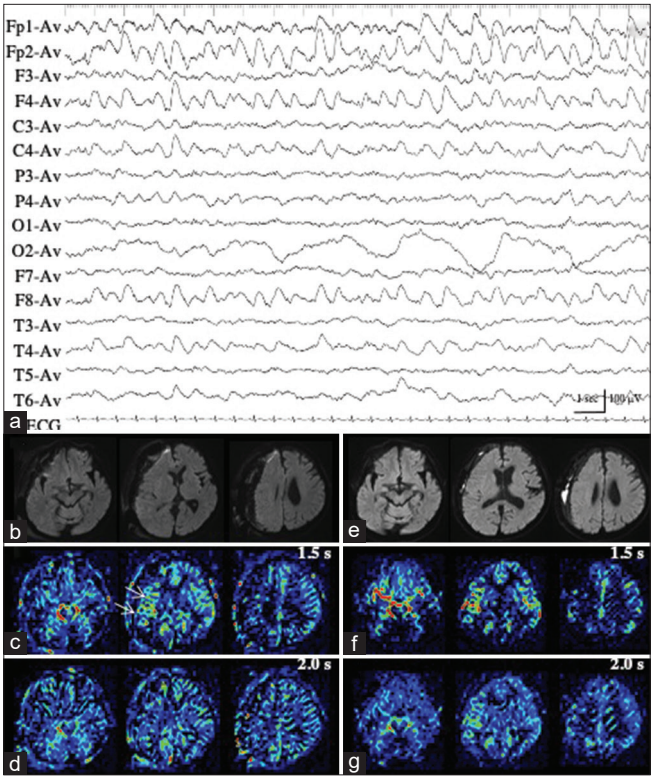

Figure 5: Patient 5. (a) Ictal EEG shows 1.9-Hz rhythmic delta activity with sharp waves in the right anterior quadrant. (b) On diffusion weighted image, the deviation of right cerebral hemisphere is still persistent. However, no parenchymal change has been noted. (c) With PASL at PLD of 1.5 sec, slightly increased area has been observed in the right frontal lobe (white arrows). (d) This finding is not apparent on PASL at PLD of 2.0 s. (e) During interictal state (a month after (a)), DWI reveals slight improvement in the deviation of the right cerebral hemisphere. (f and g) No laterality of ASL signals is observed both on PASLs at PLD of 1.5 (f) and 2.0 s (g). EEG: Electroencephalogram, DWI: Diffusion weighted image, PASL: Pulsed arterial spin labeling, PLD: Post labeling delay.

NCSE was diagnosed only from the EEG findings. Nonetheless, his condition was diagnosed as subtle SE with twitching of the left limbs. Levetiracetam was orally administered following the intravenous administration of fosphenytoin and levetiracetam. During the interictal state, the deviation of the right cerebral hemisphere gradually improved [Figure 5e], and no laterality of ASL signals was observed at PLD of both 1.5 [Figure 5f] and 2.0 [Figure 5g] sec.

Patient 6, who had an old hematoma cavity in the left fronto-parietal lobe, developed acute cerebellar infarction on the left side. Approximately 2 weeks after the onset of cerebellar infarction, his consciousness was impaired. EEG demonstrated a 1.5-Hz RDA with sharp waves in the left posterior quadrant, and a duration <10 s [Figure 6a]. On conventional MRI, we did not observe a *de novo* lesion [Figure 6b]. MRA showed slightly poor visualization of the left MCA periphery because of the old intracerebral hematoma [Figure 6c]. ASL failed to reveal ictal hyperperfusion, and revealed mildly decreased ATA at the left MCA periphery [Figures 6d and e]. No specific therapeutic intervention was prescribed based on the diagnosis of possible NCSE, and the patient spontaneously regained complete consciousness. During interictal states, ASL findings were similar to those of the ictal state [Figures 6f and g].

DISCUSSION

In this study, we used 1.5-T PASL to detect ictal hyperperfusion during NCSE in six patients. In Patients 1 and 3, 1.5-T PASL with dual PLDs of 1.5 s and 2.0 s showed the hemodynamics of ictal hyperperfusion, with a resolution comparable to that of 3-T pCASL with dual PLDs of 1.5 s and 2.5 s in our previous report.[19] In Patient 1, the highest ASL signals originated from the interhemispheric cortex of the right frontal lobe at PLD of 1.5 s, and spread to the

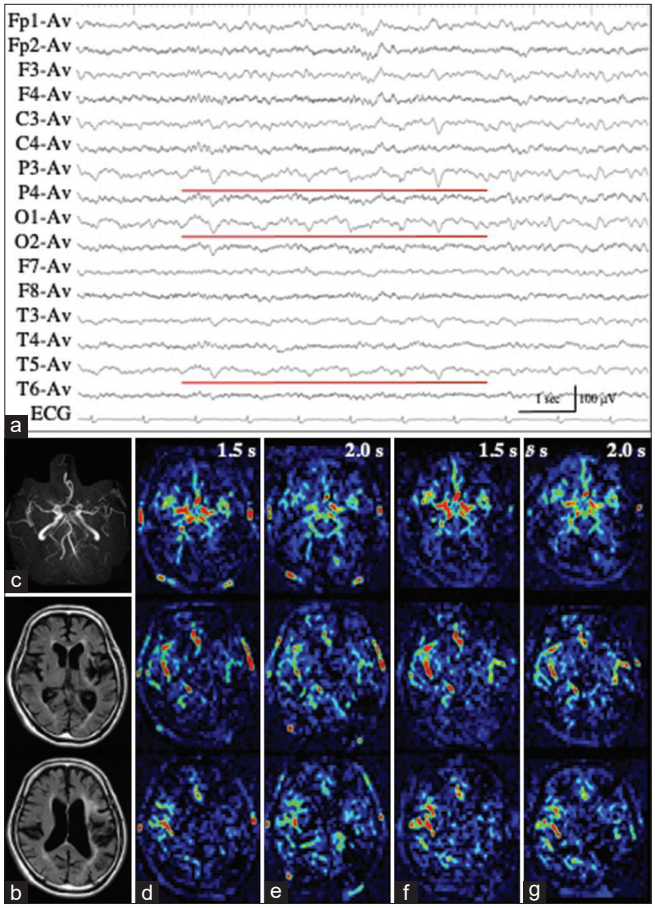

Figure 6: Patient 6. (a) Ictal EEG shows 1.5-Hz rhythmic delta activity with sharp waves in the left posterior quadrant, and a duration <10 s (red lines). (b) Fluid attenuated inversion recovery images display an old hematoma cavity in the left fronto-parietal lobe but fail to reveal a *de novo* lesion. (c) MRA shows slightly poor visualization of the left MCA periphery because of the old intracerebral hematoma. (d-g) PASL with dual PLDs reveal mildly decreased ATA of the left MCA periphery, both during ictal (d and e) and interictal states (f and g). EEG: Electroencephalogram, MRA: Magnetic resonance angiography, MCA: Middle cerebral artery, PASL: Pulsed arterial spin labeling, PLD: Post labeling delay, ATA: Arterial transit artifact.

convexity of right frontal and parietal cortices at PLD of 2.0 s, consistent with the ictal EEG findings. Furthermore, ASL signals in the contralateral hemisphere decreased probably because of the steal phenomenon of blood flow from the ictal onset side to the contralateral side[17,19] at PLD of 1.5 s; they slowly increased at PLD of 2.0 s.

The ATA of the major arteries was one of the most prominent signals on 1.5-T PASL images, which makes tissue CBF difficult to assess.[2] While the ATA of the Willis's ring can be identified by its shape, that of distal MCA can be visualized up to M3 and M4 portions, which in turn can be mistaken for the tissue CBF of the MCA territories. However, the detailed time course of blood flow in the major arteries and the epileptically activated cortex was visualized well in Patient 3. At a PLD of 1.5 s, only the ATA of the major arteries were visualized. Nonetheless, ATA decreased, and the ASL signals of the ictally activated cortex increased stepwise at PLDs of 1.8 s and 2.0 s. It was impossible to prove obvious ictal hyperperfusion at PLD of 1.5 s alone. This necessitated additional images with a longer PLD of 2.0 s to delineate ictal hyperperfusion in this patient. There was no apparent T1 shortening effect in patients 1 and 3, which indicated longer PLD of 2.0 s was suitable for delineating slower blood flow on 1.5-T PASL.

Previous our studies have shown that the detection of ictal hyperperfusion on 3-T pCASL depends on the electrophysiological intensity or power of the epileptic ictus.[13,16,17,19,21] Our findings suggested that this idea seemed to be more prominent on 1.5-T PASL than on 3-T pCASL, although the intensity of epileptic ictus cannot be accurately quantified. The intensity of RID in patient 1 and on-going periodic discharges, including LPD in patient 3, are electrophysiologically large enough to induce ictal ASL hyperperfusion.[10,11,13,16-19,21]

Nevertheless, ictal ASL hyperperfusion was not associated with the RID in patient 2 with situation-related NCSE. The amplitude of the RID was estimated to be "extremely low," based on the critical care EEG terminology proposed by ACNS.[9] Moreover, it was considered not large enough to induce ictal ASL hyperperfusion. This finding was consistent with our previous report that the ASL signal intensity of situation-related NCSE with low amplitude RID was lower than that of other localization-related focal epilepsy on 3-T pCASL.[19]

However, there are few reports on ictal ASL hyperperfusion in NCSE cases presenting with RDA. In particular, Ohtomo *et al*.[14] reported that ictal ASL hyperperfusion of the epileptically activated cortex and the thalamus were detected by 3-T pCASL in patients diagnosed with NCSE, based on Salzburg criteria. They exhibited RDA of frequencies >2.5 Hz or <2.5 Hz, albeit with subtle ictal phenomena, including twitching of the mouth or limbs and eye deviation.[12] In the present study, the frequency was <2.5 Hz in all three patients with RDA. We recorded obvious and slight increases in ASL signals at the site of RDA localization in Patients 4 and 5, respectively, diagnosed with NCSE, based on the Salzburg criteria.[12] Nonetheless, the increased ASL signal intensity was lower than that in Patients 1 and 3. In contrast, there was no ictal ASL hyperperfusion in patient 6 with possible NCSE. Therefore, the electrophysiological intensity of RDA with a frequency <2.5 Hz was weaker than that of RID and LPD, and differed between NCSE and possible NCSE. This necessitates distinguishing between NCSE and possible NCSE to determine the need for therapeutic intervention.[12]

We observed ictal hyperperfusion on MRA only in patients 1 and 3, with markedly increased ASL signals, thus supporting our idea that the development of ictal MRA hyperperfusion requires stronger power than that of ictal ASL hyperperfusion.[17] In addition, cortical hyperintensity on DWI was not observed in all patients. The cause of this phenomenon is unknown and speculative. However, there was possibly no such stronger epileptic ictus in the present study, since the development of cortical DWI hyperintensity requires stronger intensity than that of ictal ASL hyperperfusion.[10,11,13,16,17,19,21] It may also be attributed to the difference in image resolutions between 3-T and 1.5-T DWI.

The present study had some limitations. First, we performed data acquisition through visual inspection and could not quantitatively evaluate the real CBF value with PASL. Second, we did not directly compare the diagnostic abilities of 1.5-T and 3-T pCASL in detecting similar events in a particular patient. Third, continuous EEG monitoring could not be used in the present study, as with many local hospitals in Japan.[10,13,16] Even a routine EEG examination is not available outside working hours or on weekends, and the timing of EEG recording is often delayed.[10,13,16] Thus, it is thought to be meaningful to detect the ictal hyperperfusion with 1.5-T PASL during NCSE in daily clinical practice. Forth, the sample size was relatively small.

CONCLUSION

Despite the need for further studies with more sophisticated methods, such as the combined use of continuous EEG monitoring, 1.5-T PASL with dual PLDs of 1.5 s and 2.0 s could show the hemodynamics of ictal hyperperfusion in patients with RIS and LPD. However, ictal ASL hyperperfusion could not be visualized in patients with extremely low amplitude RID or RDA of frequencies <2.5 Hz.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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