

Arterial Spin Labeling Magnetic Resonance Imaging for Differentiating Acute Ischemic Stroke from Epileptic Disorders

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Background: Differential diagnosis between acute ischemic stroke (AIS) and epilepsy-related stroke mimics is sometimes difficult in the emergency department. We investigated whether a combination of diffusion-weighted imaging (DWI) and arterial spin labeling imaging (ASL) is useful in distinguishing AIS from epileptic disorders. *Methods:* The study included suspected AIS patients who underwent emergency MRI including both DWI and ASL, and who exhibited DWI high-intensity lesions corresponding to neurological symptoms. We investigated the relationship between the ASL results from within and/or around DWI lesions and the final clinical diagnosis. *Results:* Eighty-five cases were included (mean age, 71 ± 13 years; 47 men). The time from onset to the MRI examination was 493 ± 536 minutes. ASL showed hyperintensity in 13 patients, isointensity in 43, and hypointensity in 29. All ASL hyperintensities were observed in the cortex, with 4 patients (31%) presenting with AIS and 9 (69%) with an epileptic disorder. All of the AIS patients with ASL hyperintensity were diagnosed with cardioembolic stroke (4/4, 100%), with magnetic resonance angiography demonstrating recanalization of the occluded artery in all cases (4/4, 100%). In the 9 patients with an epileptic disorder, the area of ASL hyperintensity typically extended beyond the vascular territory (7/9, 78%) and involved the ipsilateral thalamus (7/9, 78%). All patients with ASL isointensity and hypointensity were diagnosed with AIS; none had epileptic disorders. *Conclusions:* Although cortical ASL hyperintensity can indicate cardioembolic stroke with recanalization, hyperintensity beyond the vascular territory may alternatively suggest an epileptic disorder in suspected AIS patients with DWI lesions.

Key Words: Magnetic resonance imaging—arterial spin labeling—acute ischemic stroke—epilepsy—stroke mimics

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Introduction

In the emergency department, it is critical to rapidly evaluate indications for thrombolytic and endovascular recanalization therapy against acute ischemic stroke (AIS), when patients exhibit acute neurological deficits. However, neurological deficits can also be caused by epileptic disorders, such as Todd's paralysis. In particular, patients with convulsive epilepsy who are not witnessed convulsing or those with nonconvulsive epilepsy are easily misdiagnosed with AIS. In fact, it has been reported that the most frequent stroke mimic (SM) treated with tissue plasminogen activator is epilepsy, followed by migraine with aura and conversion disorder.¹⁻³ Electroencephalograph monitoring is essential for diagnosing epilepsy, but it is often unavailable in emergency situations.

Diffusion-weighted magnetic resonance imaging (DWI) is the most sensitive tool available for the diagnosis of cytotoxic edema. It should be noted that some SMs can develop cytotoxic edema-like AIS and show high-intensity DWI signals.⁴ Partial epilepsy can show DWI high-intensity around an epileptogenic lesion in the perictal phase,⁵⁻¹⁰ while migraine with aura and conversion disorder usually does not show any DWI abnormalities.⁴ High-intensity DWI measurements in epilepsy patients may therefore lead to a misdiagnosis of AIS. The recently developed magnetic resonance imaging (MRI) technique of arterial spin labeling imaging (ASL) enables rapid evaluation of cerebral blood flow in 2-3 minutes without the use of exogenous contrast agents and therefore may be suitable for use in emergency settings.¹¹ AIS patients typically present with hypointensity in the affected region on ASL, while partial epilepsy patients usually show hyperintensity in the epileptically activated cortex during the peri-ictal phase.^{6,8-10} Therefore, ASL imaging may be useful for differentiating AIS from partial epilepsy in emergency situations. In the present study, we investigated whether ASL images can be used to differentiate AIS from epileptic disorder in suspected AIS patients arriving at the emergency department.

Methods

Patients

This study was performed on data collected from patients admitted to Kyushu Rosai Hospital between January 2012 and December 2013. The inclusion criteria were as follows: (1) AIS was suspected at the emergency department, because an acute neurological deficit was observed; (2) no convulsions were witnessed before admission; (3) an emergency MRI examination, including both DWI and ASL, was performed on the day of admission; and (4) high-intensity lesions were detected by DWI, consistent with neurological findings. Ethics approval was obtained from the institutional review board of Kyushu Rosai Hospital, who

waived the need for patient consent because of retrospective nature of this study.

Clinical Assessment

The final clinical diagnosis was made as follows. Ischemic stroke was determined when DWI high-intensity lesions consistent with neurological findings progressed to cerebral infarction on subsequent MRI scans. Ischemic stroke was further categorized into 4 subgroups based on the criteria modified from the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system:¹² (1) atherothrombotic brain infarction; (2) cardioembolic stroke; (3) lacunar infarction; or (4) brain infarction of other etiology. The possibility of an epileptic disorder was considered under the following conditions: (1) a convulsion was detected after admission; or (2) a medical history of epilepsy or anticonvulsant medication was discovered after admission. The diagnosis of epilepsy was made based on subsequent electroencephalographic findings and on the effectiveness of anticonvulsants.⁸⁻¹⁰

With respect to risk factors, hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, a diastolic blood pressure of ≥ 90 mmHg in the chronic stage (approximately 3 weeks after stroke onset), or as current treatment with antihypertensive drugs. Diabetes mellitus was diagnosed either using the diagnostic criteria of the Japan Diabetes Society¹³ in the chronic stage or based on a history of antidiabetic treatment. Dyslipidemia was defined as either a serum low-density lipoprotein cholesterol level of ≥ 3.62 mmol/L, a high-density lipoprotein cholesterol level of < 1.03 mmol/L, a triglyceride level of ≥ 1.69 mmol/L, or a history of antidyslipidemic medication. Atrial fibrillation was diagnosed based on electrocardiographic findings during hospitalization or on a history of atrial fibrillation. Smoking was defined as previous or current cigarette smoking.

MRI Examination

MRI of the brain with routine protocols or with ASL perfusion imaging was performed as previously described¹⁴⁻¹⁸ using a 3T-MRI unit (Signa HDxt 3.0T v23; GE Healthcare, Milwaukee, WI). Routine protocols included sequences for axial diffusion-weighted echo planar (b value, 1500 s/mm²; repetition time (TR)/echo time (TE), 6000 /min), T1-fluid-attenuated inversion recovery (TR/TE/inversion time (TI), 2050/16.1/741 ms), T2-weighted fast spin-echo (TR/TE, 4400/100 ms), and T2-fluid-attenuated inversion recovery imaging (TR/TE/TI, 9000/140/2120 ms). ASL was prepared using a 3-dimensional spiral fast spin-echo sequence with background suppression for perfusion imaging covering the entire brain. A continuous pulsed scheme was employed. Other acquisition parameters were as follows: 4 arms with 1024 points in each spiral arm; phase encoding in the z direction, 32; section thickness, 4 mm; TR, 4728 seconds

(AUTO); number of excitations, 3; and postlabeling delay time, 1.525 seconds. The acquisition time was 2 min 22 seconds.

Evaluation of the MRI findings, including DWI and ASL images, was based on visual inspection by 2 experienced radiologists (H.N. and A.N.) who were blind to the clinical data. First, DWI positivity was assessed by visual inspection and if positive, ASL measurements within and/or around DWI lesions were then evaluated and categorized as showing hyperintensity, isointensity, or hypointensity. Special attention was paid not to interpret arterial transit artifacts, which are bright intraluminal areas indicating occlusive regions or collateral flow, as indicating ASL hyperintensity.^{15,17-22} Any discrepancies between the two radiologists were subject to a tie-breaking judgement by a third rater (S.A.), and the majority opinion was used as the consensus read. We measured the diameter of DWI high-intensity lesions and classified them as either large (≥ 15 mm in diameter) or small (< 15 mm in diameter). When the major cerebral artery which accounted for the DWI lesion showed $\geq 50\%$ stenosis or occlusion by magnetic resonance angiography (MRA), it was regarded as steno-occlusive arterial lesion.

Statistical Analysis

The relationship between the ASL results and the final clinical diagnosis was evaluated by the chi-square test. The level of statistical significance was set at $P < .05$. Analyses were performed with statistical software (JMP 10; SAS Institute, Cary, NC).

Results

Out of 198 suspected AIS patients who underwent MRI including both DWI and ASL, 85 cases met the inclusion criteria and were included in this study. Their mean age was 71 ± 13 years old and 47 (55%) were men (Table 1). The final diagnosis was AIS in 74 patients (87%) and epileptic disorder in 9 (13%). There were no other etiologies accounting for SMs. All patients underwent an MRI examination on their day of admission. The time from onset to the initial MRI examination was 493 ± 536 minutes. ASL measurements within and/or around DWI lesions were of hyperintensity in 13 patients, isointensity in 43 patients, and hypointensity in 29 patients. Agreement between raters for ASL findings was excellent ($\kappa = 0.96$).

Table 1. Patient characteristics

Demographic data	
Age (years)	71 \pm 13
Male gender	47 (55%)
Risk factors	
Hypertension	57 (67%)
Diabetes mellitus	30 (35%)
Dyslipidemia	35 (41%)
Atrial fibrillation	18 (21%)
Smoking	34 (40%)
Final clinical diagnosis	
AIS	76 (87%)
Epilepsy	9 (13%)

Data are presented as mean \pm standard deviation or as the number (percentage [%]) of patients.

Abbreviation: AIS, acute ischemic stroke.

ASL hyperintensities were observed in the cortex in all 13 patients. The final diagnosis was AIS in 4 patients (31%) and epileptic disorder in 9 (69%) (Table 2). All patients diagnosed with AIS showed cortical infarction on follow-up CT or MRI scans and ASL cortical hyperintensities on initial MRI were located within the infarcted area. The infarcts of 2 patients were in the posterior cerebral artery territory, while the remaining 2 were the middle cerebral artery territory. Hemorrhagic transformation was observed in 2 patients. MRA showed no occlusive lesions of the major cerebral arteries, so recanalization of the occluded artery was suspected in all patients. All had underlying cardiac diseases and received a final diagnosis of cardioembolic stroke. Clinical details of the 4 AIS patients are summarized in Table 3, and DWI and ASL images from a representative case (Patient 1 in Table 3) are shown in Figure 1A. Among the patients with epileptic disorders, the area of ASL hyperintensity extended beyond the territory of the major cerebral arteries in 7 patients (78%) and involved the pulvinar of the thalamus in 7 (78%) (Fig 1B). In all of the patients with epileptic disorders, DWI highintensity lesions did not progress to brain infarction, but subsequently disappeared, and hemorrhagic transformation was not observed on follow-up computed tomography (CT) or MRI scans.

Forty-three patients with ASL isointensity were diagnosed with AIS; none had epileptic disorders. The most common stroke subtype except those of other etiologies was that of lacunar infarction (26%), followed by

Table 2. Relationship between ASL findings and final clinical diagnosis

ASL image findings	Clinical diagnosis		Subtype of AIS			
	AIS N = 76	Epilepsy N = 9	Atherothrombotic	Cardioembolic	Lacunar	other
Hyper-intensity N = 13	4 (31%)	9 (69%)	–	4 (100%)	–	–
Iso-intensity N = 43	43 (100%)	–	7 (16%)	7 (16%)	11 (26%)	18 (42%)
Hypo-intensity N = 29	29 (100%)	–	11 (38%)	10 (34%)	1 (4%)	7 (24%)

Abbreviations: ASL; arterial spin labeling, AIS; acute ischemic stroke.

Table 3. Summary of diagnostic information for AIS patients with ASL hyperintensity within the DWI lesion

Age/Sex	Location of infarction	Vascular territory	Hemorrhagic transformation	MRA findings	Cardiac disease
1. 68/M	Occipital lobe	L. PCA	+	No occlusion	SSS
2. 74/M	Temporal lobe	L. MCA	–	No occlusion	af
3. 55/M	Parietal lobe	R. PCA	–	No occlusion	OMI
4. 74/F	Frontal lobe	L. MCA	+	No occlusion	af

Abbreviations: af, atrial fibrillation; AIS, acute ischemic stroke; ASL, arterial spin labeling; DWI, diffusion weighted imaging; F, female; L, left; M, male; MCA, middle cerebral artery; MRA, magnetic resonance angiography; OMI, old myocardial infarction; PCA, posterior cerebral artery; R, right; SSS, sick sinus syndrome.

atherothrombotic brain infarction (16%) and cardioembolic stroke (16%) (Table 2). Patients in this group tended to show small DWI lesions (72%) and a lack of steno-occlusive arterial lesions on MRA scans (86%); a total of 58% of patients showed both of these features (Table 4). Follow-up CT or MRI scans showed infarctions consistent with DWI lesion.

Twenty-nine patients with ASL hypointensity were diagnosed with AIS; none had epileptic disorders. Common stroke subtypes were atherothrombotic brain infarction (38%) and cardioembolic stroke (34%) (Table 2). Patients in this group tended to show large DWI lesions (65%) and steno-occlusive arterial lesions on MRA scans (79%); a total of 93% of patients showed at least one of these features (Table 4). Follow-up CT or MRI scans showed infarctions consistent with DWI lesion.

Epileptic disorders were observed only in the patients with ASL hyperintensity, and a statistically significant difference was observed in the relationship between the ASL results and the final diagnosis (chi-square test, $P < .0001$). That is, ASL hyperintensity, but not iso- or hypointensity, predicted epileptic disorders.

Discussion

In the present study, we performed MRI examinations of suspected AIS patients at an emergency department and found that ASL imaging is useful for differentiating epileptic disorders from AIS. All patients with epileptic disorders showed ASL hyperintensity, and 69% of ASL hyperintensity patients had epileptic disorders. Although ASL hyperintensity could be

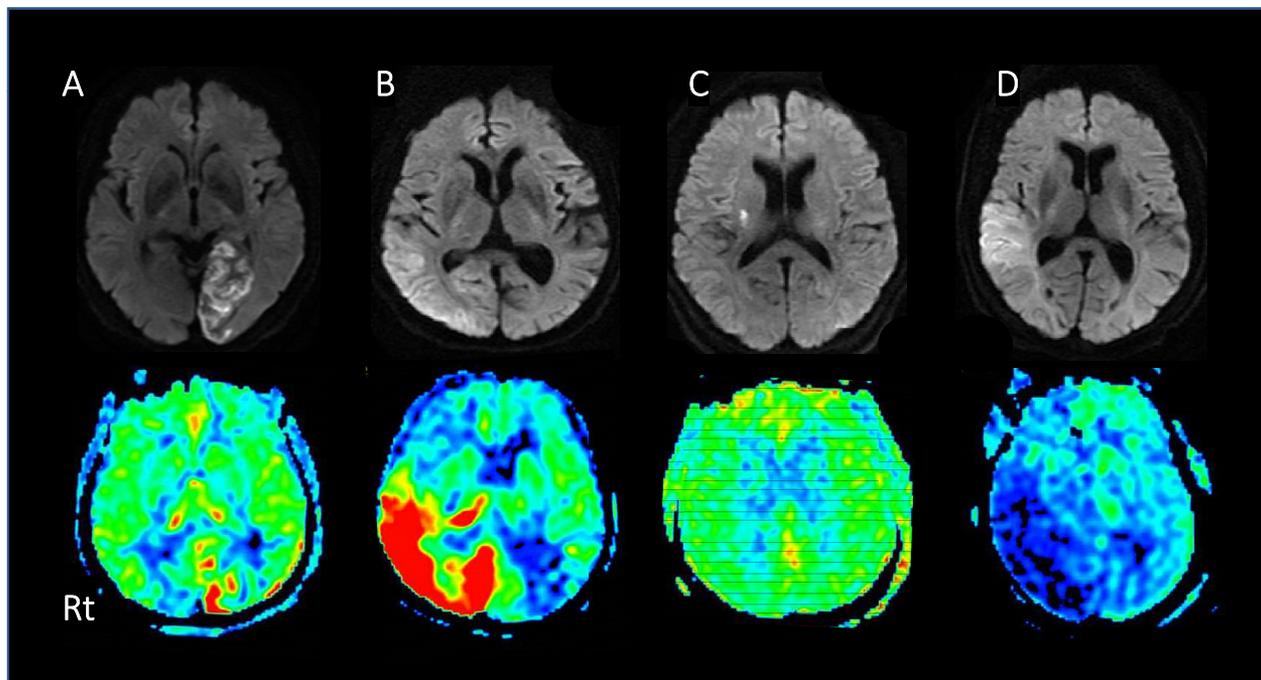


Figure 1. DWI and ASL findings from representative cases. Top: DWI image. Bottom: ASL image. (A) Cardioembolic stroke case. DWI showed high-intensity in the left posterior cerebral artery territory. ASL showed partial hyperintensity within the DWI lesion. MRA revealed no steno-occlusive lesions and recanalization was suspected. (B) Epileptic disorder. DWI demonstrated gyriform cortical hyperintensity in the right posterior temporal lobe. ASL showed hyper-intensity in the corresponding area and a lesion beyond vascular territory including the ipsilateral thalamus. (C) Lacunar infarction. DWI showed hyperintensity in the right corona radiata. ASL showed isointensity. (D) Cardioembolic stroke. DWI showed hyperintensity in the right temporoparietal lobes. ASL showed a region of hypointensity larger than the DWI lesion. Abbreviations: DWI, diffusion-weighted imaging; ASL, arterial spin labeling.

Table 4. Relationship between DWI lesion size and the presence or absence of an arterial occlusive lesion on MRA depending on ASL findings in AIS patients

ASL findings	Size of DWI lesion	MRA findings	
		Stenotic lesion	Non-stenotic lesion
Hyperintensity N = 4	Large	–	4 (100%)
	Small	–	–
Isointensity N = 43	Large	–	12 (28%)
	Small	6 (14%)	25 (58%)
Hypointensity N = 29	Large	15 (51%)	4 (14%)
	Small	8 (28%)	2 (7%)

Abbreviations: ASL, arterial spin labeling imaging; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography.

Stenotic lesion: $\geq 50\%$ stenosis or occlusion of major cerebral artery on MRA, which accounted for the DWI lesion. Large DWI lesion: at least one DWI lesion of ≥ 15 mm in diameter. Small DWI lesion: DWI lesions < 15 mm in diameter.

cardioembolic stroke with recanalization, hyperintensity occurring beyond the vascular territory can indicate epileptic disorders in suspected AIS patients with DWI lesions.

The characteristic DWI and ASL results observed for focal epilepsy in the peri-ictal phase have been explained previously according to the following stages. First, epileptogenic cortex enters an electrophysiologically extreme state and exhibits increased glucose and oxygen usage, resulting in compensatory regional hyperperfusion (ASL hyperintensity).⁸⁻¹⁰ Then, when the reactive hyperperfusion is insufficient to supply the hyperactive cortical area, cytotoxic edema occurs in epileptic cortical neurons (DWI highintensity).⁵⁻¹⁰ Such MRI findings depend on the

magnitude and duration of epileptic activity and are reversible in most cases.¹⁰ On the contrary, AIS patients typically present with ASL hypointensity in the affected region. However, this is usually not detected in patients with a small infarct, due to a low signal-to-noise ratio. ASL hyperintensity is often identified within the affected tissue when recanalization is achieved.¹⁹ Although the mechanism of ASL hyperintensity is not fully understood, loss of cerebral blood flow autoregulation (luxury hyperperfusion) and/or the changes in blood-brain barrier permeability may play a role.²³⁻²⁵ Consistent with previous reports,¹⁹ all AIS patients with ASL hyperintensity in our study showed recanalization of the occluded artery on MRA scans.

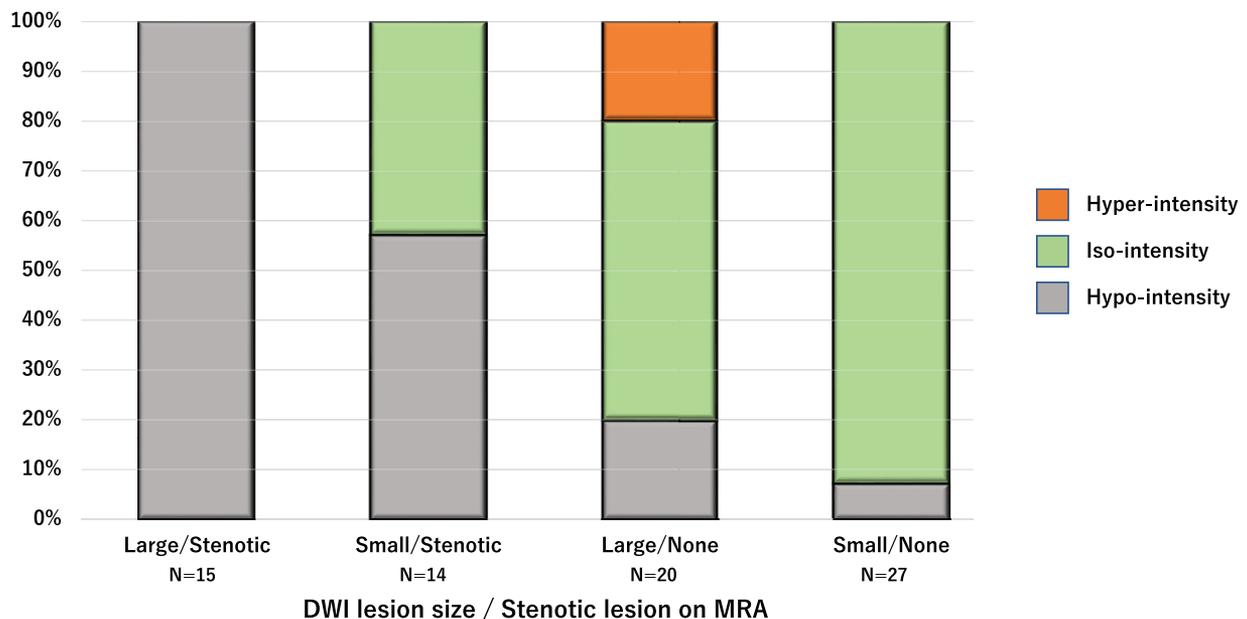


Figure 2. Dependence of ASL intensity on DWI lesion size and the presence or absence of an arterial lesion. DWI lesions were classified as large (≥ 15 mm in diameter) or small (< 15 mm). Stenotic lesion was defined as $\geq 50\%$ stenosis or occlusion of a major cerebral artery on MRA, which accounted for the DWI lesion. Abbreviations: DWI, diffusion-weighted imaging; ASL, arterial spin labeling.

Comparisons of MRI results from patients showing ASL hyperintensity have revealed a number of differences between those with partial epilepsy and those with AIS. First, DWI high-intensity lesions in epileptic disorders are usually restricted to the cortical lamina and are found around the epileptogenic lesion.⁵⁻¹⁰ In contrast, DWI high-intensity lesions in AIS can extend from the cortex to the subcortex. Second, ASL hyperintensity can extend beyond the vascular territory in epilepsy patients, while is located within the vascular territory in AIS.⁸⁻¹⁰ In patients with partial epilepsy, other structures such as the ipsilateral pulvinar of the thalamus, hippocampi, and contralateral cerebellum frequently show differences in ASL results.⁸⁻¹⁰ Third, hemorrhagic transformation can be observed in AIS accompanying ASL high-intensity regions,²⁰ but this is not usually observed in epilepsy.

Based on the DWI lesion size and the arterial stenotic lesion observed on the MRA images of the AIS patients, the vast majority (93%) of small DWI lesions (<15 mm) without arterial lesion were found to show ASL isointensity, while 57% of small lesions with arterial lesion showed ASL hypointensity (Fig 2). Although large DWI lesions (≥ 15 mm) without arterial lesion were found in all of the ASL intensity categories, large DWI lesions with arterial stenotic lesion were only of ASL hypointensity. Thus, ASL also provides additional pathophysiological information about stroke patients. Consistent with these findings, Kohno et al reported the utility of ASL in revealing the pathophysiology underlying the stroke-related hemodynamic state.¹⁹

The present study has several limitations. First, epileptic disorder was the only SM in this study. This is because we selected suspected AIS patients with DWI abnormalities, but with the exception of epilepsy, most SMs do not usually show DWI abnormalities.⁴ Second, cases of AIS presenting with onset seizure were not included in this study. Although onset seizure is relatively rare, we should be careful in diagnosing such cases, because MRI can reveal various disease-related patterns.²⁶ Finally, MRI data analysis was performed by visual inspection alone. However, this eliminated the need for special software or time-consuming analysis and therefore appears suitable for emergency medicine.

Conclusions

In this study, MRI examinations combining DWI and ASL were found to be useful for differentiating AIS from epileptic disorders during emergency situations. Cortical ASL hyperintensity can indicate cardioembolic stroke with recanalization; whereas hyperintensity beyond the vascular territory could instead suggest epileptic disorders in suspected AIS patients with DWI lesions.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.jstrokecerebrovasdis.2019.02.020](https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.02.020).

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