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Investigative Magnetic Resonance Imaging

Leak Sign on Dynamic-Susceptibility-Contrast Magnetic Resonance Imaging in Acute Intracerebral Hemorrhage

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Case Report

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Purpose: A CT angiography spot sign (CTA-spot) is a significant predictor of the early expansion of an intracerebral hemorrhage (ICH-Ex). Dynamic-susceptibility-contrast magnetic resonance imaging (DSC-MRI) can track the real-time leaking of contrast agents. It may be able to indicate active bleeding, like a CTA-spot.

Materials and Methods: From September 2014 to February 2017, we did non-contrast CT, CTA, and DSC-MRI examinations of seven patients with acute ICH. We investigated the time from symptom onset to the first contrast-enhanced imaging. We evaluated the time course of the contrast leak within the ICH at the source image of the DSC-MRI and the volume change of ICH between non-contrast CT and DSC-MRI. We compared the number of slices showing CTA-spots and DSC-MRI leaks.

Results: The CTA-spot and DSC-MRI leak-sign were present in four patients, and two patients among those showed ICH-Ex. The time from the symptom onset to CTA or DSC-MRI was shorter for those with a DSC-MRI leak or CTA-spot than for three patients without either (70-130 minutes vs. 135-270 minutes). The leak-sign began earlier, lasted longer, and spread to more slices in the patients with ICH-Ex than in those without ICH-Ex. The number of slices of the DSC-MRI leak and the number of the CTA-spot were well correlated.

Conclusion: DSC-MRI can demonstrate the leakage of GBCA within hyperacute ICH, showing the good contrast between hematoma and contrast. The DSC-MRI leakage sign could be related to the hematoma expansion in patients with ICH.

Keywords: Intracerebral hemorrhage; CTA-spot sign; DSC-MRI

INTRODUCTION

Early expansion of ICH (ICH-Ex) is associated with a significant adverse clinical outcome (1). The CT angiography spot sign (CTA-spot) has recently been accepted as an essential predictor of ICH-Ex (2-4). To improve the sensitivity of the CTA-spot, various CT techniques, such as post-contrast CT, perfusion CT, and dynamic CTA, have been used (5-8). Recently, Schindlbeck et al. reported that contrast-enhanced T1-weighted (CE-T1) and T1-dynamic-imaging (CE-T1-D) could detect spot signs like CTA-spots (9-12).

Dynamic-susceptibility-contrast magnetic resonance imaging (DSC-MRI) has been used to evaluate the perfusion status of the brain, and T2* gradient echo-planar imaging (T2*-GRE-EPI) is generally used for DSC-MRI. A hyperacute hematoma shows

central high signal intensity (SI) with a peripheral blooming dark rim on T2*-GRE-EPI. A gadolinium-binding MR contrast agent (GBCA) has a dark signal intensity on T2*-GRE-EPI due to the susceptibility effect of T2* shortening of high-concentration GBCA. If there is any active bleeding within a hyperacute ICH, it can be made visible by DSC-MRI, like the CTA-spot, CE-T1, or CE-T1-D. To the best of our knowledge, there has been no previous report of using DSC-MRI to view active extravasation in acute ICH, such as a CTA-spot sign. We recently worked with seven patients with hyperacute ICH, which was evaluated by DSC-MRI. In this paper, we describe the clinical profile and imaging findings of DSC-MRI in the seven patients, and we evaluated whether DSC-MRI could detect active bleeding with ICH.

MATERIALS AND METHODS

From September 2014 to March 2017, seven patients with acute ICH underwent DSC-MRI. All patients were admitted to our hospital within 6 hours of ictus. We obtained demographic and clinical data from each patient's medical record, including blood pressure, blood lipid profile, prothrombin time ratio expressed by the international normalized ratio, and partial thromboplastin time. In the past medical history, one patient had received antiplatelet medication after percutaneous coronary intervention, and the other six patients had never received anticoagulant or antiplatelet medication. The modified Rankin Scale (mRS) score was calculated at the time of discharge and at 90 days.

Among the CT or MRI, we carried out the imaging studies in the order of availability. MRI was done first in two patients. CT was done with precontrast CT, CTA, and 3-minute delay postcontrast CT. CTA studies are obtained from the C6 level to the vertex in the helical HS mode. Precontrast and postcontrast CT were done with the following imaging parameters: 120 kVp; 340 mA. CTA parameters are:

- 0.7 mL/kg contrast (maximum of 80 mL through an antecubital vein via an 18- or 20-gauge venous cannula);
- 5- to 10-second delay;
- 120 kVp;
- 270 mA;
- 1 second/rotation;
- 0.0625- to 1.25-mm slice thickness;
- table speed 3.75 mm/rotation.

CTA was reconstructed with axial images of 1-mm slice thickness and 2-cm thickness maximum intensity projection (MIP) images on axial, coronal, and sagittal planes with a 3 mm overlap. Precontrast and postcontrast CT were obtained with a 5-mm slice thickness without a gap. MRI was done with a 1.5 T scanner (Achieva, Philips Medical System, Best, the Netherlands) in six subjects, and with a 3.0 T scanner (Ingenia Q, Philips) in one subject. Our stroke MRI protocol was done with diffusion-weighted-imaging (DWI), DSC-MRI, FLAIR, T2*-gradient-recalled-echo (GRE), or susceptibility-weighted-imaging (SWI). DSC-MRI (T2*-GRE-EPI) was done with the following acquisition parameters:

- repetition time (TR) 2000 (1800 for 3T) ms,
- echo time (TE) 40 ms,
- flip angle 75 (90 for 3T),
- 5-mm slice thickness,
- 5 TR dummy scan before GBCA injection (9-10 sec),
- 2 mL bolus injection for 0.1 mmol/kg of gadobutrol (Gadovist, Bayer HealthCare, Germany).

The other MRI sequences were done with the following acquisition parameters:

DWI:
- TR/TE, 8900/93 ms;
- slice thickness, 5 mm;
- slice gap, 10%, b-value 1000 sec/mm^2.

T2*-weighted imaging;
- TR/TE, 630/20 ms, FA18;
- slice thickness, 5 mm;
- slice gap, 10%.

SWI: TR/TE, 17/0, FA 17, 2 mm, no gap.

FLAIR:
- TR/TE/TI (inversion time), 8800/140/2500 ms;
- slice thickness, 5 mm;
- slice gap,10%.

We investigated the time from symptom onset to the first contrast-enhanced imaging (TTI). A radiologist evaluated the location, change of ICH volume, and features of a CTA-spot sign or DSC-MRI leak sign. ICH volumes were calculated on the initial CT and follow-up CT and T2*- GRE with the previously validated ABC/2 method (13). We evaluated the volume change of ICH between first precontrast CT and T2*-GRE. In two patients in whom MRI was done first, we compared the size changes of a hematoma between the T2*-GRE and follow up CT. An increase of ICH volume more than 30% or 6 mL was considered to be a significant enlargement (3). We defined a CTA-spot sign as any small focus of enhancement within the hematoma on CTA multi-planar maximum intensity projection (MIP) images or delayed-enhanced CT images. We defined a DSC-MR

leak sign as any dark signal intensities within ICH where shape and location changed with arterial GBCA bolus over time. We evaluated the starting time and duration of the contrast leak within the ICH at the source image of T2*-GRE-EPI. We defined the leak duration as the time from the first appearance of the dark signal, which is the GBCA bolus in the ICH, to the time when the dark signal did not change its signal intensity or location. We compared the number of slices showing the CTA-spot and the number of slices to which leak on T2*-GRE-EPI spread. We evaluated microbleeds on T2*GRE or SWI and counted the total number of microbleeds.

RESULTS

Demographic and clinical data of patients are summarized in Table 1. Five patients showed deep ICH localization (three in basal ganglia, two in the thalamus), and two patients showed lobar ICH. The CTA-spot and DSC-MRI leak-sign were present in four patients, and two patients among those showed ICH-Ex. The mean TTI for CTA or DSC-MRI after symptom onset was 2 hours 30 minutes (range 70-270 minutes) on average. TTI was shorter for four patients with DSC-MRI leak and CTA-spot than for the three patients without CTA-spot or DSC-MRI leak (70-130 minutes vs. 135-270 minutes). The mean ICH volume increase in two patients with ICH-Ex was 50 ml. The leak-sign began earlier, lasted longer, and spread to more slices in the patients with ICH-Ex than in those without ICH-Ex (Figs.1, 2, and Supplementary movie 1); the mean starting time of the GBCA leak after contrast injection was 9 seconds for patients with ICH-Ex and 31 seconds for patients without ICH-Ex. The mean duration of the DSC-MRI leak was 36 sec in patients with ICH-Ex and 12 sec in patients without ICH-Ex. Although the shape and location of DSC-MRI leaks and CTA-spots were not precisely the same, the number of slices of a DSC-MRI leak and the number of CTA-spots were well correlated. In four patients who showed DSC-MRI leak signs, the shape and location of the leak sign changed

Table 1. Summary of Clinical and Imaging Data

Parameters	Leak (+) ICH-Ex (+) (n=2)	Leak (+) ICH-Ex (−) (n=2)	Leak (−) ICH-Ex (−) (n=3)
Age	79, 86	75, 79	58, 65, 68
Blood pressure	(180/100), (160/90)	(217/114), (174/100)	(203/120), (210/110), (152/77)
PT INR/ PTT	0.93/22.6, 1.16/52.7	1.1/27, 1/25.5	1/23.7, 1/27.6, 1.1/26.6
TG/LDL/HDL (mean)	68.5/76.5/53.5	112/114/60	48/106/54.7
ICH location	Frontal/BG (IVH + both)	BG/Th (IVH + both)	Th (IVH +)/BG/Parietal
Initial volume (mL)	14.1, 18.2	16.9, 29.8	18, 18.9, 46.6
F/U volume (mL)	60.5, 71.2	18.2, 30	18, 23.8, 51.6
TTI (min)	130, 70	100, 75	200, 270, 135
Time to leak (sec)	10, 8	26, 46	N/A
Leak duration (sec)	26, 46	8, 16	N/A
# Slices of leak	7, 7	1, 1	N/A
# CTA spot	7, 8	2, 2	N/A
# CMBs	16, 26	3, 13	13, 3, 2
mRS 3 month	5, 5	3, 3	5, 4, N/A

PT INR/PTT: prothrombin time ratio by the international normalized ratio (0.88-1.28), partial thromboplastin time (23-35 sec).
TG/LDL/HDL: Triglycerides (0-150 mg/dl)/low-density (0-130 mg/dl)/high-density lipoprotein cholesterol (40-60 mg/dl)
TTI: time to contrast enhanced imaging (CT or MRI) from symptom onset.
CTA-spot: number of total CTA-spots
Time to leak: starting time of the GBCA leak after contrast agent injection.
Leak duration: duration of leaking (changing the shape of GBCA leak)
# Slices of leak: the number of slices to which GBCA leak spread.
CTA spot # CMB: the number of CTA spots and cerebral microbleeds
mRS: modified Rankin scale score at 90 days

dynamically within ICH. When compared to CT, the leak in a DSC-MRI early phase was relatively consistent with the location of CTA-spot signs and the location of the leak in the DSC-MRI late phase showed good correlation with that of the delay-CT (Fig. 3). In patients with ICH-Ex, the leak on the DSC-MRI spread over seven slices, and an average CTA-spot number was 7.5 in these patients. In patients without ICH-Ex, the DSC-MRI leak was found in 1 slice, and the CTA-spot number was 2. The mean number of microbleeds was 21 in two patients with ICH-Ex and 6.8 in five patients without ICH-Ex. The 3-month mRS score was 5 for two patients with ICH-Ex and median 3 (3-5) for patients without ICH-Ex.

DISCUSSION

The CTA-spot sign has recently been accepted as an essential predictor of ICH-Ex (2-4). The spot sign indicates the presence of active bleeding within an ICH. Although detection of a bleeding spot by CTA is rapid and relatively simple, the sensitivity of CTA for detecting a spot sign has not been satisfactory. A multicenter, prospective study revealed the sensitivity of CTA spot-sign detection for predicting significant ICH-Ex to be 51% (3). To improve the sensitivity of the CTA-spot sign, different CT techniques, such as the delayed post-contrast CT, perfusion CT, and dynamic CTA, have been used (5-8). In their studies, the CT techniques improved the detection of contrast leakage within a hematoma and increased the sensitivity to approximately 90%. According to the results of dynamic
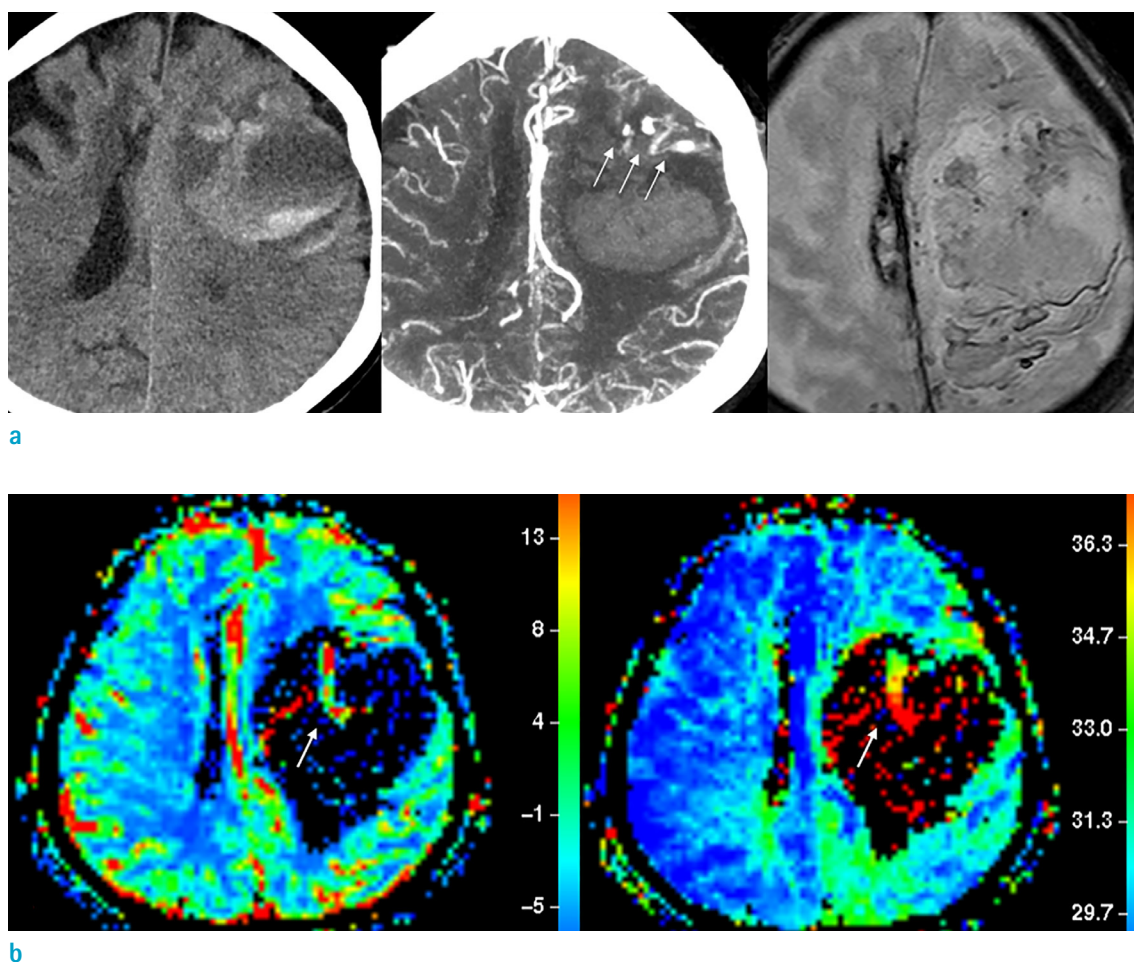
Fig. 1. A 79-year-old patient with ICH-Ex. (a) Initial precontrast brain CT (right) showing acute ICH (14.1 mL) in the left frontal lobe. Initial CTA axial MIP image (middle) showed multiple CTA-spot signs (arrows) in the anterior portion of ICH. On gradient-echo MRI (left), the ICH significantly increased (60.5 mL), and mild midline shifting had developed. (b) The reconstructed rCBF map (right) and the TTP map (left) revealed GBCA leakage (arrows).
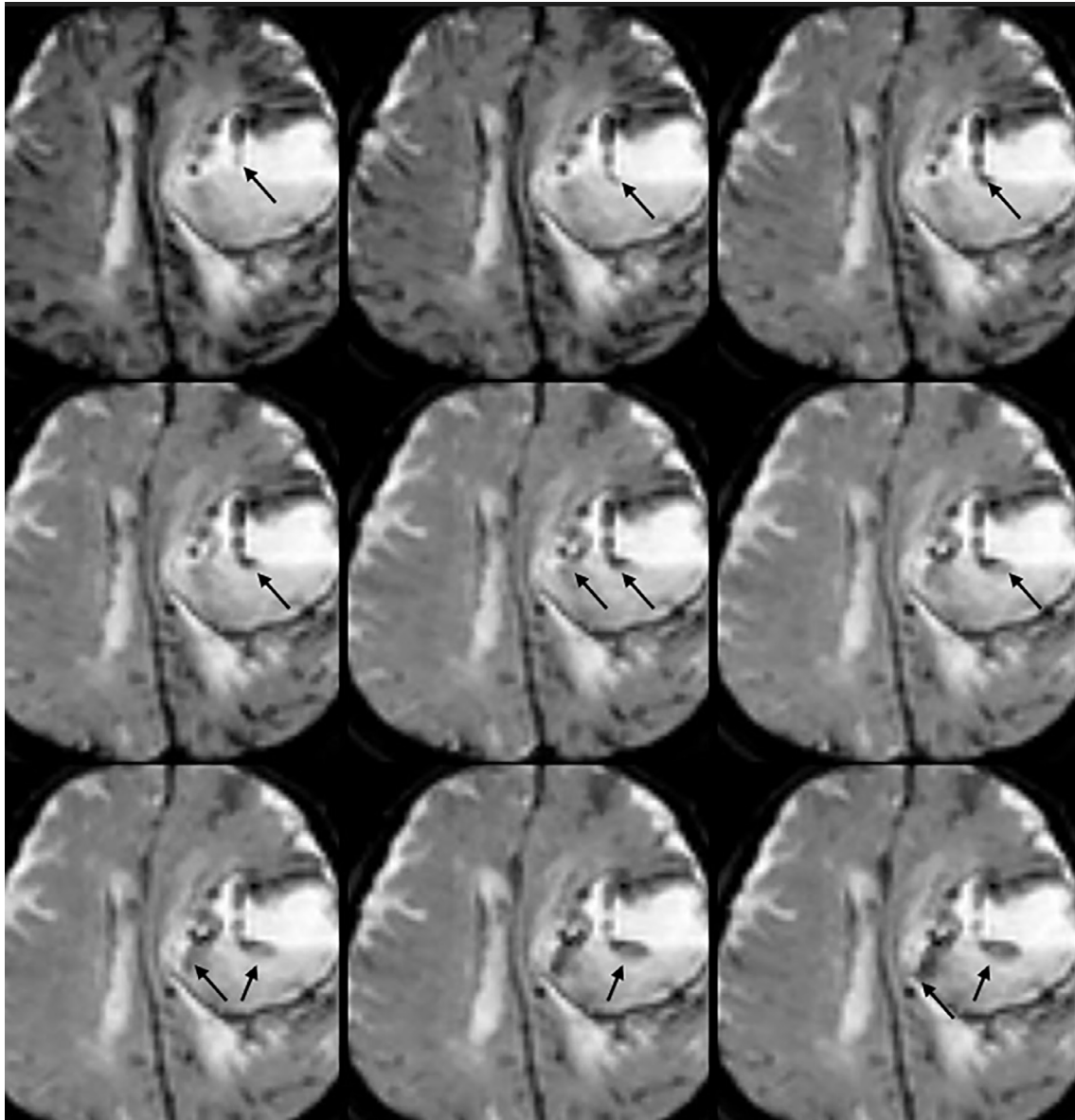
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Fig. 1. (c) The T2*-GRE-EPI of the DSC-MRI clearly showed active GBCA leakage in the central area of the ICH. The time interval between images was two seconds. The GBCA had dispersed and continued to spread within the hematoma (arrows).

CTA and perfusion CT, the median time for the peak CTA-spot attenuation was 30.8 and 50 seconds, respectively, following intravenous injection of the contrast agent, and ranged from 24 to 63 seconds (5, 7). This time may be slightly later than the acquisition time of first-pass CTA, which is usually 20-26 seconds (7). Therefore, first-pass CTA may not allow sufficient time for spot visualization and may, therefore, miss the delayed spot sign in some patients.

Although this is a small case series, DSC-MRI could demonstrate real-time GBCA leaks within the ICH, and the

contrast of DSC-MRI between a hematoma and leaking GBCA was quite acceptable. Acute ICH usually shows a high density on CT, and the CTA-spot sign also has high density. Therefore, a minimal leak of iodine-based contrast agents may be hard to recognize by visual assessment. On DSC-MRI, the largest portion of a hyperacute ICH shows high SI, and a GBCA leak appears as a dark signal on T2*-GRE-EPI. The contrast of DSC-MRI between a hematoma and a GBCA leak is undoubtedly better than that seen on CTA. Another advantage of DSC-MRI is the real-time visualization of
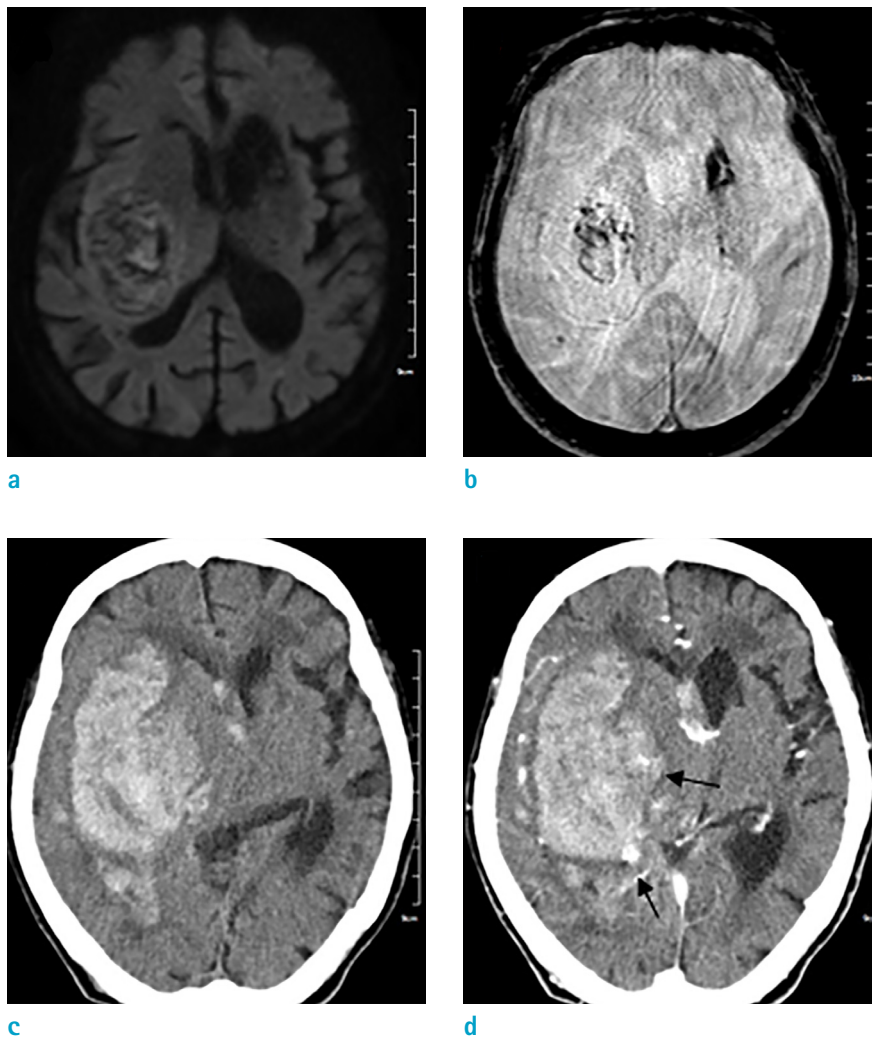
Fig. 2. An 86-year-old patient with ICH-Ex. (a, b) Initial DWI and GRE were showing acute ICH (18.2 mL) in the right basal ganglia. The ICH significantly increased (71.2 mL) on the follow-up CT (c), and delayed enhanced CT (d) showed enhancing spot signs (arrows).

a circulating GBCA and the extended temporal window, which is sufficient not only to detect the spot sign but also to observe the temporal and spatial evolution of the spot sign within the ICH. In four patients with a DSC-MRI leak (+) and CTA spot sign, TTI was shorter than that of the patients without a leak (70-130 min vs. 135-270 min), and this result is similar to those in previous studies (3, 10, 14). In our study, the time to leak in the patients with a DSC-MRI leak (+) was slightly earlier than on the previous CT studies (mean 22.5 sec, range 8-46 sec). This difference may result because the contrast between the leaked contrast agent and hematoma is superior with MRI than with CT. In two patients with ICH-Ex, the GBCA leak began earlier (mean 9 sec vs. 31 sec), and this result is comparable with the multiphase CTA study (14). In the CTA-spot sign study, not all patients with spot signs had ICH-Ex. In one prospective multi-center observational study (3), the positive predictive

value and sensitivity for ICH-Ex of the CTA-spot sign were 61% (95% CI, 47-73) and 51% (95% CI, 39-63). Another study (2) suggested that three or more CTA-spot signs could be a predictor of ICH-Ex. In our study, two patients without ICH-Ex had a DSC-MRI leak sign that was shorter and had only two CTA-spot signs. Perhaps the ICH-Ex is related to the severe degree of extravasation. When the extravasation is weak, the ICH-Ex might not occur.

Since our study was a small case series, we need more clinical experience using DSC-MRI for detecting the spot sign in acute ICH, and further imaging sequences such as CE-T1 may be required to complement DSC-MRI, especially if TTI is more delayed than 4-6 hours when ICH may have dark SI on DSC-MRI. In T1WI, hyperacute ICH usually has iso-SI, and a GBCA leak may appear as a bright spot on CE-T1 (9-12). Finally, in terms of the radiation hazards, MRI may be preferable to CTA or another combined CT
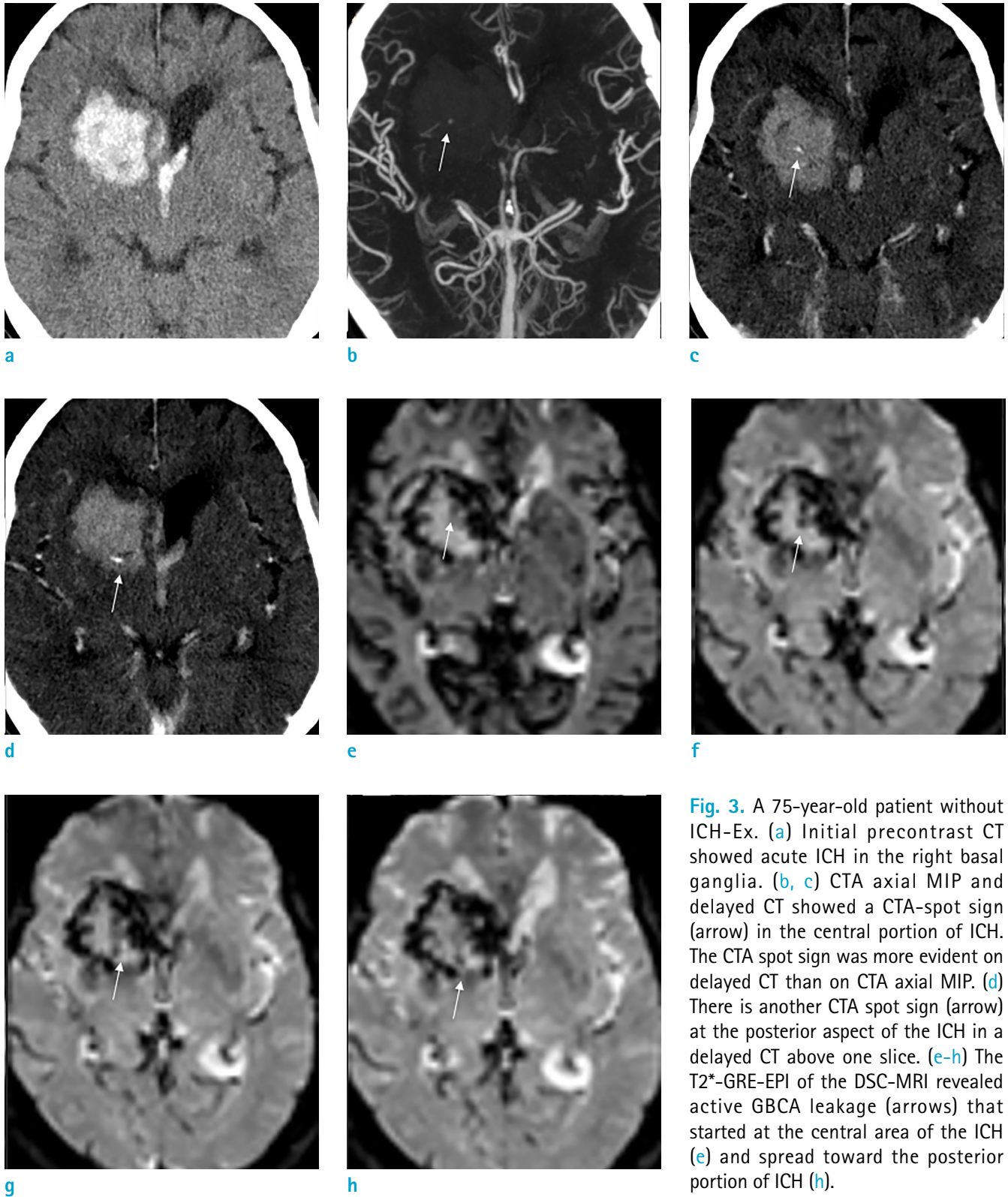
Fig. 3. A 75-year-old patient without ICH-Ex. (a) Initial precontrast CT showed acute ICH in the right basal ganglia. (b, c) CTA axial MIP and delayed CT showed a CTA-spot sign (arrow) in the central portion of ICH. The CTA spot sign was more evident on delayed CT than on CTA axial MIP. (d) There is another CTA spot sign (arrow) at the posterior aspect of the ICH in a delayed CT above one slice. (e-h) The T2*-GRE-EPI of the DSC-MRI revealed active GBCA leakage (arrows) that started at the central area of the ICH (e) and spread toward the posterior portion of ICH (h).

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technique. Although an MRI examination requires a longer acquisition time than does a CT examination, and may not be a possible option for an unstable patient, a combination of limited sequences, such as DSC-MRI, T2*-GRE, and CE-T1WI with a fast imaging technique, can reduce the acquisition time to less than 5 minutes.

In conclusion, our case series demonstrated a real-time GBCA leak within hyperacute ICH with the use of DSC-MRI. Although MRI has limitations for severely ill patients, DSC-MRI may be an option for detecting the leakage of GBCA within hyperacute ICH.

Conflicts of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Approval (include appropriate approvals or waivers)

This study was done in accordance with the Declaration of Helsinki (1964) and its later amendments. This study was approved by Institutional Review Board.

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