Spot Sign in Acute Intracerebral Hemorrhage in Dynamic T1-Weighted Magnetic Resonance Imaging

Katharina A. Schindlbeck, MD; Anna Santaella, BSc; Ivana Galinovic, PhD; Thomas Krause, MD; Andrea Rocco, PhD; Christian H. Nolte, MD; Kersten Villringer, MD; Jochen B. Fiebach, MD

Background and Purpose—In computed tomographic imaging of acute intracerebral hemorrhage spot sign on computed tomographic angiography has been established as a marker for hematoma expansion and poor clinical outcome. Although, magnetic resonance imaging (MRI) can accurately visualize acute intracerebral hemorrhage, a corresponding MRI marker is lacking to date.

Methods—We prospectively examined 50 consecutive patients with acute intracerebral hemorrhage within 24 hours of symptom onset. The MRI protocol consisted of a standard stroke protocol and dynamic contrast-enhanced T1-weighted imaging with a time resolution of 7.07 s/batch. Stroke scores were assessed at admission and at time of discharge. Volume measurements of hematoma size and spot sign were performed with MIRcron.

Results—Contrast extravasation within sites of the hemorrhage (MRI spot sign) was seen in 46% of the patients. Patients with an MRI spot sign had a significantly shorter time to imaging than those without (P<0.001). The clinical outcome measured by the modified Rankin Scale was significantly worse in patients with spot sign compared with those without (P≤0.001). Hematoma expansion was observed in the spot sign group compared with the nonspot sign group, although the differences were not significant.

Conclusions—Spot sign can be detected using MRI on postcontrast T1-weighted and dynamic T1-weighted images. It is associated with worse clinical outcome. The time course of contrast extravasation in dynamic T1 images indicates that these spots represent ongoing bleeding. (Stroke. 2016;47:00-00. DOI: 10.1161/STROKEAHA.115.011570.)

Key Words: acute stroke imaging ■ intracerebral hemorrhage ■ MRI ■ spot sign ■ stroke hemorrhagic ■ T1 dynamic

Intracerebral hemorrhage (ICH) accounts for ≈20% of all strokes and is associated with high mortality and major neurological impairments.1,2 Therapeutic options are limited, and the European Stroke Organisation guidelines recommend acute stroke unit care, intensive blood pressure monitoring, intermittent pneumatic compression in immobile patients, and secondary prevention with blood pressure lowering for ICH survivors based on moderate- to high-quality evidence.3 Decompressive craniectomy might reduce mortality in patients with supratentorial ICH and needs to be investigated in larger prospective cohorts.4 Compared with ischemic stroke, ICH has a significantly worse clinical outcome,5 especially in those patients with hematoma growth within the first few hours.6 Hence, there is a continuing search for reliable imaging markers of active hemorrhage and consecutive hematoma expansion. Wada et al7 found tiny, enhancing foci within acute hematomas (spot sign) in source images of computed tomographic angiography (CTA), which correlated with an increased risk of hematoma expansion. Successive studies demonstrated that both spot sign on CTA source images and contrast extravasation (CE) in postcontrast CT predict mortality and poor clinical outcome in patients with primary ICH.7–11 Several prospective studies in patients with acute ICH could show that the spot sign in CTA is a predictor of hematoma expansion.8,12–14 Improved sensitivity for predicting hematoma expansion and poor outcome in patients with ICH and spot sign were recently shown with an additional 90-second delayed CTA acquisition in a prospective single-center study.15

No equivalent magnetic resonance imaging (MRI) marker for acute ICH has been established to date, although MRI can accurately detect acute and chronic ICH and is increasingly being used in acute stroke imaging.16,17 There is no study investigating clinical outcome and CE in ICH based on MRI. Therefore, we studied CE in T1-weighted and T1 dynamic imaging at 3 T MRI to investigate whether CE within the hematoma can be detected, presumably indicating ongoing
bleeding. We hypothesized that the spot sign observed in contrast-enhanced T1-weighted MRI is associated with worse clinical outcome and hematoma growth.

Methods

Sample

All patients admitted to our clinic presenting within 24 hours of stroke syndrome onset underwent an MRI protocol during daytime. Data were obtained within a substudy of the 1000Plus study (NCT00715533). All patients gave written informed consent. Because of regulatory enforcement, family members were not allowed to decide on study participation. Inclusion criteria were clinical diagnosis of a stroke syndrome, onset within 24 hours before MRI measurement, a radiologically proven ICH, and a complete protocol with contrast agent administration (Gadovist, Gadobutrol, 10 mL; Bayer Pharma Healthcare, Germany). Therefore, patients in clinically unstable condition or who had contraindications for contrast agent administration could not participate in the study. Furthermore, patients with incomplete protocols (n=18), severe motion artifacts (n=7), or ICH because of secondary pathogenesis, like underlying neoplasia (n=4), trauma (n=1), hemorrhagic venous infarct (n=1), or hemorrhagic conversion of ischemic stroke (n=1) were excluded. Between September 2009 and December 2014, 50 patients were ultimately included in the study. Demographic and clinical data were collected from the patients’ chart, including time window, hematoma pathogenesis, neurological symptoms, in-hospital mortality, hematoma localization, blood pressure on admission, blood glucose, prothrombin time ratio expressed by the international normalized ratio, and creatinine on admission. National Institutes of Health Stroke Scale (NIHSS) was assessed by a certified neurologist at the time of admission and discharge. The modified Rankin Scale (mRS) score was performed at the time of discharge.19

Image Acquisition

In all subjects, MRI was performed with a 3 Tesla (T) Scanner (TIM Trio; Siemens). Diffusion-weighted images (DWI; repetition time TR/echo time TE, 8900/93 ms; slice thickness, 2.5 mm; slice gap, 0%), T2*-weighted imaging (TR/TE, 620/20 ms; slice thickness, 5 mm; slice gap, 10%), time-of-flight magnetic resonance angiography (TR/TE, 22.3/86 ms; slice thickness, 0.7 mm; slice gap, −27.5%), fluid-attenuated inversion recovery sequence (TR/TE, 8000/100 ms; slice thickness, 5 mm; slice gap, 0%), and pre- and postcontrast T1-weighted imaging (TR/TE, 250/46.46 ms; slice thickness, 5 mm; slice gap, 10%) were acquired as part of our standard stroke protocol. In most patients (n=38), the protocol was amended by a contrast-enhanced dynamic T1, providing measurements of signal enhancement as a function of time, with the following acquisition parameters: TR/TE 50/2.46 ms, scan time 3 minutes 32 seconds, flip angle=25°, field of view=220 mm, resolution 7.07 x/batch, 210 dynamic images acquired over 7 slices with a slice thickness of 5 mm. The sequence was manually positioned to cover the area of the hematoma. The enhancement kinetics can be used to extract semiquantitative information regarding injured vessels or the blood–brain barrier.

Image Analysis

The evaluation of the hematoma and the presence of a spot sign were performed visually by 2 certified radiologists. To differentiate spot sign from CE because of secondary causes, the diagnostic process was based on a protocol including intracranial magnetic resonance angiography, fluid-attenuated inversion recovery sequence, DWI, and T1-weighted images. CE identification was investigated in 2 consecutive steps. First, an experienced radiologist investigated the presence or absence of the spot sign visually at the time of the patient’s MRI examination. Second, an independent rater, an experienced radiologist (Dr Fiebach), who was blinded to the clinical condition of the patient and the initial radiological report, judged the presence or absence of the spot sign.

Assessment of the hematoma volume in DWI was performed using MIRcron (Chris Rorden’s MIRcron, version 4AUG2014). In patients without DWI (n=4), we delineated the hematoma on T2*-weighted images, correcting afterward for the 18.9% of volume overestimation as suggested for this sequence by Schellinger et al.20 Furthermore, T1 postcontrast images were used for the delineation of the spot sign. Cerebral microbleeds (CMBs) were rated for presence, number, and anatomic distribution. According to the number of CMBs, they were divided into 4 groups: no CMB, single CMB, 2 to 4 CMBs, and ≥5 CMBs, similar to previous studies.21,22 The localization of CMBs was further categorized in lobar, deep, and infratentorial according to the Microbleed Anatomic Rating Scale.23

Statistical Methods

The Statistical Package for Social Sciences (SPSS Version 22) was used for data management and processing. Means and standard deviations were determined for normally distributed data, whereas medians and interquartile ranges (IQRs) were used to describe the remaining data. To compare patients with and without spot sign, the Mann–Whitney U test was used for continuous variables and the χ² test for dichotomous or categorical variables. Correlations between the volume of the spot sign and the volume of the hematoma or clinical outcome were assessed with the Spearman correlation coefficient. To determine the consistency among raters in detecting the spot sign, we performed inter-rater reliability analysis using kappa statistics. All tests were 2-tailed, and the significance cut-off was P<0.05.

Results

Fifty patients, presenting within 24 hours with an acute stroke syndrome, had acute ICH and fulfilled the inclusion criteria. Demographic and clinical patient data are summarized in Table. The mean time to imaging (TTI), meaning the approximate time from symptom onset to the MRT examination, in all patients was 7.2 hours; 56% presented within 4.5 hours and 64% within 6 hours. Sixty-four percent of all patients showed deep hematoma localization, whereas 36% were lobar. Two patients died in hospital (4%). CMBs were present in 46% (n=23) of all ICH patients. Regarding the severity, 54% had no CMBs, 10% showed a single CMB, 8% showed 2 to 4 CMBs, and 28% showed ≥5 CMBs. Lobar location was present in 47.8% (n=11) of the patients and deep or infratentorial in 52.2% (n=22).

Spot Sign

CE within the hematoma (spot sign) was observed in 23 of 50 (46%) patients with ICH. Inter-reader agreement for the identification of the spot sign was excellent with kappa=0.92 (P<0.001).

In the majority of the patients, we observed a tiny spot of CE (Figure 1A and 1B), whereas some patients (n=5) showed multiple foci of CE within the hematoma (Figure 1C). The median volume of the spot sign was 0.17 mL (IQR, 0.15–1.52). The volume of the spot sign correlated with the baseline volume of the hematoma (r=0.63; P=0.001) and correlated moderately with the outcome based on mRS (r=0.536; P=0.008). To analyze the different patterns of spot sign, we compared patients with small (<1 mL; n=18) and large (≥1 mL; n=32) spot signs. The TTI and the NIHSS at admission did not differ significantly among patients with different patterns of spot sign. Patients with large spot signs were characterized by larger hematoma volumes (median 36 versus 5; P=0.004) and worse outcome based on mRS (median 5 versus 4; P=0.003).
The presence, number, and anatomic distribution of CMBs did not differ significantly between ICH patients with or without spot sign.

**Outcome**

The patients were dichotomized according to the presence or absence of a spot sign. The clinical outcome measured by mRS in patients with spot sign was significantly worse compared with those without spot sign (median 4, [IQR, 3–4] versus 2 [IQR, 1–4]; \(P\leq0.001\); Figure 2). The NIHSS on admission did not differ significantly between the groups (spot sign: median 7.0 [IQR, 5–11] versus nonspot sign 4.5 [IQR, 2–9]; \(P=0.087\)). Both patients, who died at the hospital, were spot sign–positive.

The median hematoma volume of all patients at baseline was 10 mL (IQR, 4.75–19.25) and did not differ in patients with or without a spot sign (10 mL [IQR, 6–20] versus 10 [IQR, 4–19]; \(P=0.565\); Figure 3). The TTI was significantly different in patients with and without a spot sign: mean TTI in the spot sign group was 3.4 hours compared with 10.5 hours in the nonspot sign group (\(P\leq0.01\)). 91.3% of the patients with evidence of a spot sign presented within 6 hours of symptom onset (\(P\leq0.01\)). However, 1 patient, presenting after 15 hours of symptom presentation, was spot sign–positive.

**Follow Up**

We analyzed all patients who underwent a follow-up examination, either with CT or with MRI, within 72 hours of baseline.
Several patients had no consecutive follow up because of unstable condition or death (n=1) as a result of critical illness. Follow-up volumes were analyzed in 25 out of 50 patients, 13 patients with and 12 patients without spot sign, respectively. A case of expansion is shown in Figure 4.

Compared with the group of patients without a follow-up scan, patients with follow-up images had a significantly shorter time to baseline image (with 8.1 hours ±8.4 versus without 10.5 hours ±8.8; P=0.001) and worse outcome measured with mRS (with 2.9±1.5 versus without 2.5±1.5; P=0.015), but showed no significant differences regarding age, baseline NIHSS, baseline hematoma volume, or blood pressure on admission.

The median hematoma follow-up volume in patients with spot sign was 7 mL (IQR, 3.5–29.5 mL) compared with the initial volume of 5 mL (IQR, 4–16.5 mL). Among patients without a spot sign, the median follow-up volume was 8 mL (IQR, 5–16 mL) in accordance with the initial volume of 8 mL (IQR, 5–20 mL). However, spot sign patients showed no significant hematoma enlargement in the follow-up evaluation compared with patients without spot sign (P=0.150).

Discussion

In a prospective observational study of 50 patients with acute ICH (<24 hours), 46% showed tiny spots of CE within the hematoma. Our results indicate that spot sign in acute ICH can be diagnosed with contrast-enhanced dynamic T1-weighted MRI at 3 T. Patients with spot sign had a significantly worse outcome measured with mRS compared with those without spot sign in unadjusted comparison. The time course of CE in dynamic T1 image series indicates that the spots represent...
ongoing bleeding. However, there was no significant difference regarding hematoma expansion between the 2 groups.

The spot sign, as described by Wada, is defined as ≥1 small foci of enhancement within the hematoma on CTA source images and is therefore seen in the early phase of CTA. In CT, it is possible to distinguish spot sign in the early phase of CTA from CE in postcontrast CT. The spot sign might represent contrast leakage either from the primary ruptured or from a secondary injured vessel into the hematoma. CE on postcontrast CT was more sensitive than the spot sign on CTA in predicting hematoma expansion.

Although MRI and CT are based on entirely different physical principles, the pathophysiological processes underlying CE in acute ICH might presumably be similar for both techniques. In MRI, as well as in CTA, a fixed dose of contrast agent (10 mL of a 1 molar gadolinium containing and 80–100 mL of an iodinated contrast agent, respectively) is given to the patient independently of body weight and therefore slightly above the regular dosing in both techniques in most settings. The accumulation of contrast material in the ruptured vessels leads to increased longitudinal relaxation rate and consequently increased signal intensity in T1-weighted images. In contrast to CTA, in T1-weighted MRI, there is no contrast enhancement within the vessel. Hence, MRI is more conservative because it can only detect leakage of the contrast agent from a damaged vessel. Furthermore, the dynamic contrast-enhanced T1 sequence allows the detection of contrast accumulation over the whole 3.5 minutes scan time, whereas CT enables either the early or the delayed acquisition. With regards to the timing, the postcontrast T1-weighted imaging is comparable to the delayed acquisition in CT. Despite assumed similarities of the CE process in different imaging modalities, the mechanistic nature of the spot sign may not be identical in MRI and CTA.

MRI spot sign was found with a frequency of 46% within a time window of 24 hours. Spot sign frequency in acute ICH based on CTA ranged between 18% and 56% considering different time windows. In a prospective multicenter study, 30% of the acute ICH patients presenting <6 hours from symptom onset were spot sign–positive. Two other prospective studies with a defined time window of <6 hours showed a spot sign frequency of 33% and 22% based on CTA. The significantly shorter TTI in patients with spot sign contributes to the assumption that the spot sign is reflecting an ongoing bleeding from a ruptured vessel. This is more likely to be found in the first 6 hours after symptom onset. In T1-weighted images, hyperacute hematoma has almost the same intensity as cerebral parenchyma, so that CE within the hematoma can be detected visually and, therefore, might result in a lower detection threshold compared with CTA. Furthermore, differences in the amount of contrast agent given in CT and MRI might possibly result in a differing detection threshold of CE within the ICH.

The clinical outcome (mRS) at discharge was significantly worse in patients with spot sign compared with those without a spot sign, whereas the NIHSS at admission did not differ between the 2 groups. The significantly higher score of the NIHSS at discharge is further contributing to these results. To date, there are no other studies investigating the relationship between CE and clinical outcome in ICH using MRI. Our findings are in line with previous studies on ICH based on CT, showing that the presence of the spot sign is independently associated with poor clinical outcome.

In addition to worsening outcome, spot sign in CTA is associated with hematoma enlargement. A recent prospective multicenter study could show that CTA spot sign is a predictor of hematoma expansion in acute ICH. Using CTA, postcontrast-enhanced CT and perfusion, d’Esterre et al demonstrated that hematoma expansion was especially associated with the early phase of extravasation in acute ICH. Aviv et al created an animal model of CE in acute ICH in swine using dynamic contrast-enhanced MRI to provide real-time information of CE to allow the estimation of contrast leakage rate. In humans, there is only one study describing CE in MRI as a marker of ongoing hemorrhage in acute ICH. They found a significant correlation of CE and hematoma enlargement.
using 0.2 T MRI. In our study, hematoma expansion was observed in the spot sign group compared with the nonspot sign group; however, these differences were not significant. This might be because of our small sample size of follow-up cases, representing only 50% of the original sample.

Limitations
The limitations of this study are its observational design and the absence of long-term follow-up. The study suffers from unadjusted comparison as a result of small sample size. Furthermore, selection bias was present in patients unable to undergo MRI because of unstable medical condition or nighttime admission and the regulatory enforcement of informed consent, which can only be provided by the patient. The absence of a fixed follow-up protocol results in a possible selection bias because of the clinical decision for follow-up imaging. However, a fixed follow-up protocol is difficult in this observational setting because it would require an enforcement of imaging exams even in critically ill patients. Therefore, our results concerning hematoma growth are limited and should be investigated within an interventional clinical trial. In the majority of the patients, we compared MRI baseline images with CT follow-up images. Even though quantification on DWI correlates well with hematoma size on CT, it does not totally match.20

Seen from a methodological point of view, CE in T1 sequences is not exclusively because of leakage from a vessel but is also seen in disruption of the blood–brain barrier. Compared with digital subtraction angiography, a reliable differentiation between these 2 phenomenon is ultimately not possible; however, this concern accounts for both MRI and CT. Further evaluation with greater cohorts embedded in randomized control trials is needed to confirm a possible hematoma growth in patients with spot sign based on MRI.

Conclusions
We conclude that spot sign can be diagnosed in acute ICH with contrast-enhanced dynamic T1-weighted MRI at 3 T and is associated with worse clinical outcome. Spot sign on MRI can identify patients at risk and could be used as an imaging marker.

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Abstract

ダイナミック T1 強調 MRI における急性脳内出血のスポット サイン

Spot Sign in Acute Intracerebral Hemorrhage in Dynamic T1-Weighted Magnetic Resonance Imaging

Katharina A. Schindlbeck, MD1; Anna Santaella, BSc2; Ivana Galinovic, PhD3, et al.

1 Department of Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany; 2 International Graduate Program Medical Neurosciences, Berlin, Germany; and 3 Center for Stroke Research Berlin (CSB), Berlin, Germany

背景および目的: 急性脳内出血のCT画像では、CT血管造影（CTA）におけるスポットサインが血腫拡大および不良な臨床転帰のマーカーとして確立されている。破壊共鳴画像法（MRI）では急性脳内出血を正確に描写できるが、現時点で上記に相当するMRIのマーカーはない。

方法: 急性脳内出血発症後24時間以内の連続患者50例を前向きに検討した。MRI撮像プロトコールは、標準的な脳卒中プロトコール、および時間分解能が7.07s/batchのダイナミック造影T1強調画像とした。入院時と退院時に脳卒中スコアを評価した。MRlcronにより血腫サイズおよびスポットサインの体積を測定した。

結果: 患者の46%で出血部位内の造影剤の漏出（MRIスポットサイン）が認められた。MRIスポットサインが認められた患者では、スポットサインが認められなかった患者に比べて撮影までの時間が有意に短かった（P < 0.001）。スポットサインが認められなかった患者と比較して、スポットサインが認められた患者では改良Rankin Scale（mRS）により評価した臨床転帰が有意に不良であった（P < 0.001）。スポットサインが認められなかった患者群と比較して、スポットサインが認められた患者群では脳腫脹拡大が見られたが、有意差はなかった。

結論: スポットサインはMRIの造影後T1強調画像およびダイナミックT1強調画像で検出することができ、臨床転帰不良と関連する。ダイナミックT1強調画像における造影剤漏出の経時的変化から、これらのスポットが進行性の出血であることが示唆される。


図1 造影後T1強調画像で描出された出血およびスポットサイン。患者3例の造影後T1強調MRIの軸位断面。A: 血腫内の造影剤漏出（CE）の小さいスポット（白矢印）、撮影までの時間（TII）は2.33時間、米国国立衛生研究所脳卒中スケール（NIHSS）は10であった。B：血腫内のCEの小さいスポット（白矢印）、TIIは1.37時間、NIHSSは6であった。C：多発性のCE（白矢印）、TIIは0.98時間、NIHSSは21であった。