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SHORT COMMUNICATION

Early Hemolysis Within Human Intracerebral Hematomas: an MRI Study

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Abstract

Early hemolysis occurs in the hematoma within 24 h in rat model of intracerebral hemorrhage (ICH). The present study investigated the prevalence of early hemolysis in ICH patients using MRI and the relationship between early hemolysis and perihematomal edema. Thirty ICH patients were prospectively enrolled within 24 h of onset. All patients had cranial CT on admission. Cranial MRI with T2 FLAIR-weighted imaging and T2*-weighted imaging were undertaken at days 1 and 14. The evolution of a non-hypointense lesion on T2*-weighted images and the relationship between the volume of that non-hypointense lesion and perihematomal edema volume were investigated. MRI images of 15 patients were analyzed. The median hematoma volume was 16.3 ml on admission. All patients underwent a baseline MRI within 24 h of ICH onset and showed a non-hypointense lesion within the hematoma on T2*-weighted images. The volume of non-hypointense lesion on T2*-weighted image was 6.0 (8.9) ml at day 1 and 8.6 (17.3) ml at day 14. The absolute perihematomal edema volume was 16.0 (17.9) ml and 24.8 (27.5) ml at days 1 and 14, respectively. There was a linear correlation between non-hypointense T2* lesion and perihematomal edema volume at day 1 and day 14 ($p < 0.01$). Early hemolysis in the hematoma occurs in humans and contributes to the development of perihematomal edema.

Keywords Cerebral hemorrhage · Magnetic resonance imaging · Brain edema · Hemolysis

Introduction

Intracerebral hemorrhage (ICH) is a life-threatening neurological emergency with high mortality and morbidity [1, 2]. As red blood cells lyse, hemoglobin and the resultant iron overload cause secondary brain injury including perihematomal edema [3]. Recently, in a rat model of ICH, erythrolysis was found within the hematoma as early as the first day of ICH [4]. However, whether early erythrolysis also occurs in human ICH has not been determined.

Magnetic resonance imaging (MRI) has the potential to reveal the hemorrhagic brain injury because of its high sensitivity for iron-containing compounds. The iron atoms shorten the relaxation times, leading to hypointensity on spin-echo and gradient-echo T2-weighted images in brain regions with higher iron content.

The manifestation of hematomas on MRI depends largely on the age of the hematoma, hemoglobin status (oxy- and deoxyhemoglobin), and the integrity of red blood cells [4, 5]. Reports have shown that hyperintense signal occurred within hematoma [6, 7]. In our recent experimental study, we found a non-hypointense on T2* image in the hematoma occurs in rat models of ICH at day 1. Histologically, marked erythrolysis occurs in the core of the hematoma with the formation of erythrocyte ghosts [4]. Also, the diameter of erythrocytes decreased significantly in the clot at the first 24 h in a pig ICH model [8]. Therefore, erythrolysis may happen earlier than previously reported, resulting in a hyperintense T2* signal in the center of hematoma.

The present study investigated the prevalence of early hemolysis in the clot in ICH patients using MRI and the relationship between early hemolysis and perihematomal edema evolution.

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Methods

Inclusion and Exclusion Criteria

The study was approved by ethics committee of Peking University Health Science Center-Michigan University Joint Institute. Consecutive men and non-pregnant women > 18 years with a primary supratentorial hematoma between 5 and 30 cm^3 who admitted within 24 h after symptoms onset were included after obtaining informed consent from the patients or their surrogates. Exclusion criteria were inability to undergo MRI owing to metallic objects or unstable medical condition, systemic diseases with limited life expectancy, secondary ICH (hemorrhage resulting from aneurysm, vascular malformation, hemorrhagic infarction, tumor, or impaired coagulation), and surgical or stereotactic hematoma evacuation/thrombolysis, primary/secondary intraventricular hemorrhage, and unconsciousness.

Clinical Assessments

Demographic data (age, gender), presence of vascular risk factors (hypertension, diabetes, smoking, and alcoholism), and clinical characteristics (NIHSS, Glasgow coma scale, modified Rankin Scale, and treatment) were prospectively collected. Blood pressure was measured before every MRI scanning.

Imaging Protocol

All patients underwent non-contrast head computed tomography (CT) on admission. MRI was performed on a 3.0-T scanner (GE Discovery MR750) using a four-channel head coil at 24 ± 12 h and 14 ± 3 days with the following pulse sequences: T2 fluid-attenuated inversion recovery-weighted images (T2 FLAIR-weighted images: TR = 8000 ms, TE = 103.0 ms) and GRE-T2* W (T2*-weighted images: TR = 340 ms, TE = 20 ms).

Image Analyses Hematoma volume (H_v) was measured on the admission CT by using the ABC/2 method. Measurements of the MRI images were independently done by two investigators who were blinded to clinical data using MRIcro software. Perihematomal edema (PHE) volumes were measured on T2 FLAIR-weighted images at day 1 and day 14. The examiner manually drew regions of interest (ROIs) by tracing the perimeters of the hematoma and perihematomal edema in each slice through the hemorrhagic lesion (Fig. 2a). The traced ROIs in contiguous voxels were then summed up after adjusting for the slice thickness to yield a hematoma volume and absolute PHE volume. Relative perihematomal edema volume (RHE) was calculated as absolute edema volume divided by hematoma volume at day 1 [9, 10]. The total lesion and the non-hypointense lesion volumes inside the hematoma were also measured on T2*-weighted image at day 1 and day 14. The percentage of non-hypointense T2* lesion was

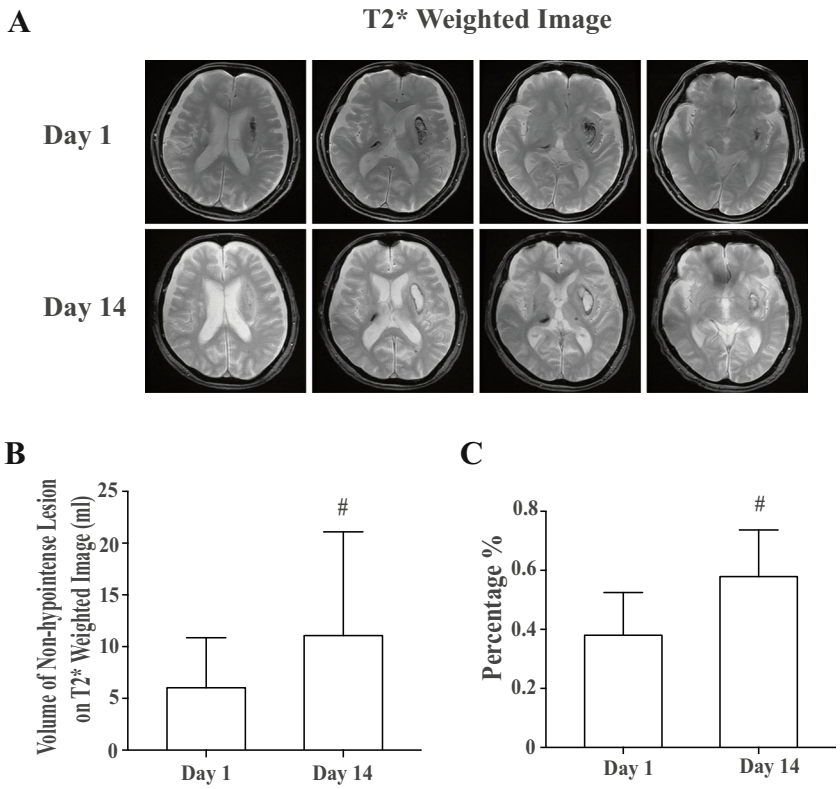

Fig. 1 **a** Representative T2*-weighted images of a left basal ganglion hematoma at days 1 and 14. Note the heterogeneity within the hematoma including a non-hypointense area. **b** The volume of the non-hypointense lesion on T2*-weighted image at day 1 and day 14. Values are mean ± SD, $^{\#}p < 0.01$. **c** Dynamic evolution of the non-hypointense lesion, expressed as a percentage of total lesion, on T2*-weighted images from day 1 to day 14, $^{\#}p < 0.01$

expressed as the non-hypointense T2* lesion volume at day 1 or day 14 over the total T2* lesion volume at day 1.

Statistical Analysis

Categorical variables are shown as numbers and percentages. Continuous variables are expressed as means ± SD or median values [interquartile range] as appropriate. Tests performed were the Student *t* test or the Mann-Whitney *U* test for continuous variables as appropriate. Paired *t* tests were applied to test for the difference of brain edema and non-hypo T2* lesion between day 1 and day 14. Linear regression models were used to test for correlations assessed with non-hypointense T2* lesion volume and the corresponding PHE volume. A value of $p < 0.05$ was considered significant.

Results

Patient Characteristics

A total of 30 patients with ICH were enrolled between January and November 2014. Seventeen patients underwent a baseline MRI within 24 h. One patient was excluded due to poor image quality of the second MRI. One patient missed the second MRI. The selection resulted in 15 patients with deep ($n = 12$) and lobar ($n = 3$) ICH. The mean age was 61 ± 13 years old,

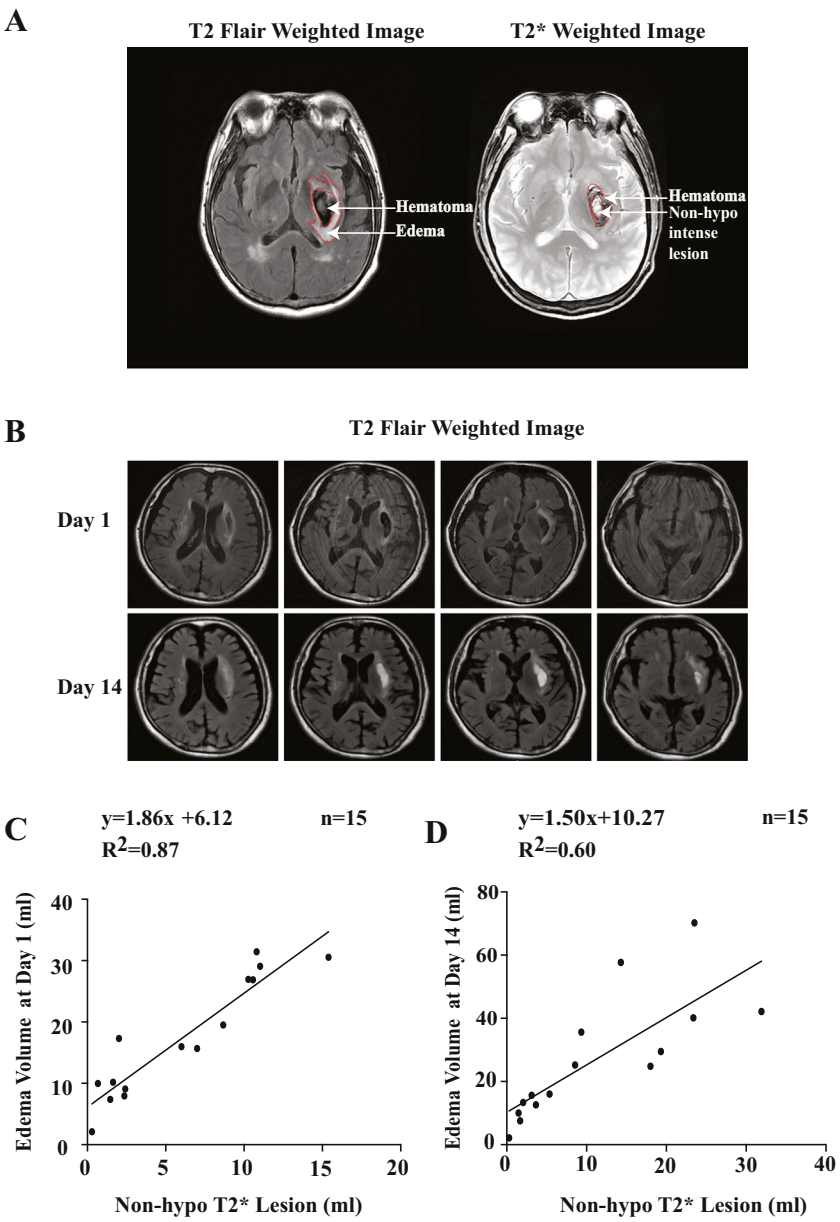

Fig. 2 **a** Representative pictures of ROI measurements on T2 FLAIR-weighted image and T2*-weighted image. **b** Representative pictures of hematoma and perihematomal edema at day 1 and day 14 on T2 FLAIR-weighted image. **c** Scatter plot showing the correlation between perihematomal edema (PHE) and non-hypointense lesion of T2*-weighted image at day 1 ($R^2 = 0.87$, $n = 15$, $p < 0.01$). **d** Scatter plot showing the correlation between PHE and non-hypointense lesion on T2*-weighted image at day 14 ($R^2 = 0.60$, $n = 15$, $p < 0.01$)

with 14(93%) male patients. Nine (60%) patients had hypertension and two (13%) had diabetes. The median NIHSS score was 6 (7) on admission. All patients had a diagnostic CT scan at day 1. The median hematoma volume was 16.3 (13.2) ml. All patients received intravenous mannitol before this MRI. The mean systolic blood pressure was 162 ± 33 mmHg on admission. The mean diastolic blood pressure was 99 ± 18 mmHg on admission. The systolic blood pressures were less than 160 mmHg when they took baseline MRI and 140 mmHg when they took follow-up MRI.

The Characteristics of Non-Hypointense Lesion on T2*-Weighted Image at Day 1

The hematomas showed hypo-, iso-, or hyperintense signals on T2*-weighted images. At day 1, all patients showed non-hypointense signals in the center of the hematoma on T2*-weighted images. At day 14, there was a significant enlargement of the non-hypointense lesion (Fig. 1a).

The volume of non-hypointense lesion on T2*-weighted image was 6.0 (8.9) ml at day 1, which increased to 8.6 (17.3) ml at day 14 ($p < 0.01$, Fig. 1b). The percentage of non-hypointense lesion to total T2* lesion was 38.1 ± 15.5% at day 1, and this increased to 57.9 ± 15.8% at day 14 ($p < 0.01$, Fig. 1c).

The Relationship Between Non-Hypointense Lesion on T2*-Weighted Image and Perihematomal Edema

The absolute PHE volume (Fig. 2a) gradually increased from day 1 to day 14 on T2 FLAIR-weighted images (Fig. 2b). The absolute PHE volume was 16.0 (17.9) ml at day 1 and 24.8 (27.5) ml at day 14 ($p < 0.01$, Fig. 2b). The relative PHE was 2.32 ± 0.57 at day 1 and 3.12 ± 1.19 at day 14. There was a linear relationship between the non-hypointense lesion volume on T2*-weighted image and the absolute PHE at day 1 (Fig. 2c) and day 14 (Fig. 2d) ($R^2 = 0.87$, $n = 15$, $p < 0.01$ at day 1; $R^2 = 0.60$, $n = 15$, $p < 0.01$ at day 14).

Discussion

There were three findings in this study: (1) the appearance of the hematomas on T2*-weighted imaging is heterogeneous with a non-hypointense core that may reflect hemolysis; (2) early hemolysis occurs within the hematoma during the first day after ICH in patients; (3) early hemolysis was linearly correlated with perihematomal edema.

Erythrocyte lysis contributes to brain edema formation. Intracerebral infusion of hemoglobin or erythrocyte lysate causes brain edema within 24 h, but infusion of packed erythrocytes only causes edema after about 3 days [3, 11]. In this study, the volume of the non-hypointense lesion on T2*-weighted image was closely correlated to perihematomal edema at day 1 and day 14. This suggests that early hemolysis in the hematoma may also contribute to early brain edema in ICH patients. In our study, mannitol was given to all patients before the baseline MRI. Further study is needed to elucidate the relationship between therapy and brain edema and hemolysis. Currently, a phase II trial is examining whether an iron chelator, deferoxamine, can reduce ICH-induced brain injury (ClinicalTrials.gov Identifier: NCT02175225). Our findings suggest that it might be advantageous to give deferoxamine as soon as possible after ictus.

In the current study, the relative PHE ranged from 2.32 to 3.12 from day 1 to day 14. This increase was much lower than relative PHE from the CT study. In cranial CT scan, brain edema was calculated as thin layers sequentially outward from the edge of the hematoma. It was believed that after ICH onset, the hematoma volume shrinkages showing as a decreased volume of hyperintensity mass. However, which is the real edge of hematoma remains controversial. Whether the hyperintensity mass on CT scans at 1 or 2 weeks after ICH can precisely predict the hematoma size still needs to be determined. However, in MRI-based study, the baseline hematoma volume at day 1 was used when calculating relative PHE. So the increase of relative PHE was less obvious in MRI-based study than that in the CT-based study.

In conclusion, the current study provides radiological evidence that early hemolysis also occurs in human ICH patients, although this needs histological confirmation. Such early hemolysis contributes to the development of perihematomal edema. Future studies should determine whether early hemolysis in the clot also contributes to worse functional outcome in ICH patients.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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