Temporal Pattern of Cytotoxic Edema in the Perihematomal Region After Intracerebral Hemorrhage
A Serial Magnetic Resonance Imaging Study

Na Li, MD, PhD; Hans Worthmann, MD; Meike Heeren, MD; Ramona Schuppner; Milani Deb, MD; Anita B. Tryc, MD; Eva Bue1lmann, MD; Heinrich Lanfermann, MD; Frank Donnerstag, MD; Karin Weissenborn, MD; Peter Raab, MD

Background and Purpose—Knowledge about cytotoxic edema (CE) in intracerebral hemorrhage is still limited. We aimed to analyze its presence, temporal pattern, and prognostic meaning.

Methods—Twenty-one patients with primary intracerebral hemorrhage underwent magnetic resonance imaging at days 1, 3, and 7 after symptom onset. CE was identified using diffusion-weighted imaging. Hematoma and perihematomal edema volumes were measured on fluid-attenuated inversion recovery images. National Institutes of Health Stroke Scale score was assessed at admission and with each magnetic resonance imaging. Clinical outcome was assessed by modified Rankin scale at 90 days.

Results—CE appeared in half of the patients within the first 24 hours. The apparent diffusion coefficient values decreased until day 3 and were significantly reversed from days 3 through 7 (P<0.01). Patients with CE showed significantly faster perihematomal edema growth from day 0 to 1 (P=0.036) than those without. Larger 3-day perihematomal edema volume (P=0.02) and presence of CE on day 3 (P=0.07) were associated with poor clinical outcome.

Conclusions—CE is associated with stroke severity, perihematomal edema volume, and poor outcome. It is considered to indicate ongoing neuronal injury and, thus, might emerge as new treatment target. (Stroke. 2013;44:1144-1146.)

Key Words: cytotoxic edema ■ diffusion-weighted ■ ICH ■ MRI ■ perihematomal edema

During the first days after primary intracerebral hemorrhage (ICH), secondary brain injury develops caused, among other things, by perihematomal edema (PHE). Although vasogenic (extracellular) edema is commonly described in the perihematomal regions, the existence of cytotoxic (intracellular) edema (CE) is controversially discussed.1–4 Some previous diffusion-weighted imaging (DWI) studies in ICH patients showed CE in the perihematomal area in some parts of them.1–3

We aimed to investigate prospectively the presence and temporal pattern of CE within the first week after ICH and its impact on clinical outcome.

Methods

Patients

Patients >18 years of age with primary ICH proven by computed tomography scan who presented within 24 hours of symptom onset were prospectively included. Exclusion criteria were secondary ICH, contraindication to magnetic resonance imaging, surgical ICH procedure, or refusal of participation. Demographic and clinical data were collected at admission, and clinical outcome was assessed by modified Rankin scale on 90 days. Informed consent was obtained from patients or relatives. The study has been approved by the local ethics committee.

Imaging Protocol and Analysis

Magnetic resonance imaging was performed within 24 hours, 72±12 hours, and 7±1 days after symptom onset. The imaging protocol included the following: gradient-echo T2* imaging, 3-dimensional (3D)–fluid-attenuated inversion recovery images, and triplanar DWI (online-only Data Supplement). Hematoma and edema volume were measured by manual segmentation on 3D-fluid–attenuated inversion recovery-data using ITK-SNAP analysis software.5 Apparent diffusion coefficient (ADC) maps were calculated by the scanner software. Areas of increased DWI-b1000-signal and reduced ADC value by >10% compared with mirror region of interest were interpreted as CE and manually outlined; if located outside of the ICH on T2*- and DWI-b0-images, regardless of the T2-signal on fluid-attenuated inversion recovery. This was confirmed by a 3D-multiplanar localization function of the image analysis software (Figure 1).
Statistical Analysis

Between-group comparisons were done using Fisher exact test for categorical variables, and Student t test or Mann–Whitney U test for continuous variables as appropriate. Within-group comparisons of ADC and relative ADC values and the PHE volumes at different time points were analyzed by repeated ANOVA. *P<0.05 was considered significant.

Results

Twenty-one patients were prospectively enrolled. Clinical data are shown in Table I in the online-only Data Supplement. Magnetic resonance imaging was performed in 20 patients on day 1 (15±9 hours), 19 on day 3 (2.9±0.5 days), and 18 on day 7 (7.0±0.9 days). Baseline hematoma volume was measured on day 1 in 19 patients, and in 2 cases with missing or distorted 1-day data on 3-day fluid-attenuated inversion recovery images.

Temporal Profile of CE

CE was detected in 9 of 20 (45%) cases on day 1. It was still present on day 3 in all cases available (1 dropout) and disappeared in 2 cases on day 7. In another case, CE appeared on day 3 and remained until day 7. The location of CE is shown in Table II in the online-only Data Supplement. Eight of 10 patients with CE at any time point had complete follow-up. Their mean ADC value was decreased by 28% (557±121×10−6 mm²/s) relative to the mirror region of interest on day 1, by 39% (487±87×10−6 mm²/s) on day 3, and by 19% (630±112×10−6 mm²/s) on day 7. According to repeated ANOVA, both ADC *(P=0.032)* and relative ADC values *(P=0.016)* significantly changed during the first week after ICH. In pairwise comparisons, the values significantly reversed from day 3 to 7 *(P=0.002 and P=0.003, respectively; Figure 2).*

Presence of CE on day 1 *(P=0.031)* and 3 *(P=0.020)*, but not day 7 *(P=0.112)*, was significantly associated with higher National Institutes of Health Stroke Scale score at admission. CE was significantly associated with larger PHE volume on day 1 *(P=0.036)*, but not on day 3 *(P=0.055)* or day 7 *(P=0.553; Figure 3A).* PHE growth from day 0 to 1 was significantly faster in patients with CE than in those without *(P=0.036)*, whereas it did not differ between the groups thereafter (days 1–3: *P=0.318; day 3–7: *P=0.606; Figure 3B).* According to repeated ANOVA, PHE volume growth was significantly attenuated in patients with CE *(P=0.014)* and tended to be in patients without CE *(P=0.057) during the first week after ICH. In pairwise comparisons, in patients with CE, the PHE growth from day 3 to 7 was significantly smaller compared with that from day 0 to 1 *(P=0.029)* and 1 to 3 *(P=0.037).*

Association of PHE and CE With Clinical Outcome

At 90-day follow-up, 12 patients showed favorable (modified Rankin scale: 0–3) and 9 unfavorable outcomes (modified Rankin scale: 4–6). Patients with CE on day 3 tended to develop unfavorable outcome *(P=0.07).* PHE volume on day 3 was larger in patients with unfavorable than in those with favorable outcome *(P=0.020).* Baseline hematoma volume was not associated with outcome *(P=0.213).*

Discussion

CE represents restricted diffusion because of cellular swelling mostly referred to failure of ATP-dependent ion transport. Our data are in line with the concept that CE is a reversible step in cellular dysfunctional process if compensatory mechanisms, such as ionic channel or ATP pump activity, are still effective.* Accumulated evidence suggests a nonischemic metabolic crisis surrounding the hematoma.⁷–⁹ Brain tissue samples
of patients who had been operated on within 72 hours after ICH showed mitochondrial dysfunction in the perihematomal region, which was thought to contribute to a reduction in oxidative metabolism and the use of oxygen in this region. A transient focal increase in perihematomal glucose metabolism was observed 2 to 4 days postictus and resolved on day 7. The time pattern of these metabolic changes is in line with the CE changes in our study.

The association of CE with stroke severity at admission and larger hematoma and PHE volume are consistent with previous DWI studies. Importantly, we showed that the presence of CE was accompanied by faster PHE growth within the first 24 hours. In our study, poor 90-day clinical outcome was significantly associated with larger PHE volume on day 3 and tended to be associated with pronounced CE on day 3, but not with baseline hematoma volume. This finding implies that secondary brain injury might play a significant prognostic role in ICH patients with small-to-medium hematomas. Former studies showing a risk of unfavorable outcome in ICH patients with CE appearance within 6 to 24 hours support this assumption. Experimental and clinical studies suggested that local compression, diaschisis, and toxic clot components, such as thrombin and hemoglobin degradation compounds, are responsible for perihemorrhagic tissue damage. Such ongoing neuronal injury may, therefore, represent an important therapeutic target after ICH.

**Disclosures**

None.

**References**


**Figure 3.** Temporal profile of perihematomal edema (PHE) volume and PHE volume growth in patients with and without cytotoxic edema (CE). Patients with CE: black triangles, solid trend line; patients without CE: open circles, broken trend line. (A) PHE volume in patients with qualified fluid-attenuated inversion recovery (FLAIR) images at any time point (day 1: n=17; day 3: n=18; day 7: n=18). Difference between patients with and without CE: day 1: P=0.036; day 3: P=0.055; day 7: P=0.553. (B) PHE volume growth in patients with qualified FLAIR images at all 3 time points (n=13). PHE growth between patients with vs without CE (day 0–1: P=0.036; day 1–3: P=0.318; day 3–7: P=0.606). Repeated ANOVA showed change of PHE volume growth in patients with CE (P=0.014) and without CE (P=0.057) during the first week after intracerebral hemorrhage. Pairwise comparisons showed larger PHE growth in patients with CE for comparison of day 0 to 1 vs 3 to 7 (P=0.029) and day 1 to 3 vs 3 to 7 (P=0.037).
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Stroke. 2013;44:1144-1146; originally published online February 7, 2013;
doi: 10.1161/STROKEAHA.111.000056

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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