Hyperacute injury marker (HARM) in primary hemorrhage

A distinct form of CNS barrier disruption

C.S. Kidwell, MD
R. Burgess, MD, PhD
R. Menon, MD
S. Warach, MD, PhD
L.L. Latour, PhD

Address correspondence and reprint requests to Dr. Chelsea S. Kidwell, Department of Neurology and Georgetown Stroke Center, 4000 Reservoir Road, NW, Building D, Suite 150, Georgetown University Medical Center, Washington, DC 20007
ck256@georgetown.edu

ABSTRACT

Objective: The objective of the study was to characterize a previously unreported form of CNS barrier disruption in intracerebral hemorrhage (ICH): hyperacute injury marker (HARM).

Methods: In this retrospective cohort analysis of patients presenting with primary ICH, precontrast and postcontrast MRI scans obtained within 5 days of symptom onset were analyzed. The presence of CNS barrier disruption was defined by 1) perihematomal or intrahematomal enhancement visualized on postcontrast T1-weighted MRI or 2) HARM: sulcal or ventricular hyperintensity visualized on postcontrast fluid-attenuated inversion recovery sequences (graded on a 5-point scale).

Results: Forty-six patients were included in the analysis. Mean age was 65 years, median NIH Stroke Scale score was 7, and mean ICH volume was 12.2 mL (range 0.3–46.9 mL). HARM was visualized in 85% of patients, and this was moderate to severe in 50%. In all cases, the sulcal enhancement was noncontiguous with the hematoma. Of those patients with postcontrast T1-weighted imaging, perihematomal or intrahematomal contrast enhancement was visualized in 75% of patients.

Conclusions: This study demonstrates that HARM occurs in intracerebral hemorrhage and that it likely represents a second type of CNS barrier disruption distinct from parenchymal postcontrast T1-weighted enhancement. Similar to T1 enhancement, this phenomenon may serve as a clinically useful biomarker to test therapies aimed at stabilizing acute ICH and CNS barrier disruption. Future studies are needed to further define the time course and prognostic implications of this finding. *Neurology*® 2011;77:1725–1728

GLOSSARY

BBB = blood–brain barrier; **BCSFB** = blood–CSF barrier; **DWI** = diffusion-weighted imaging; **GRE** = gradient echo; **HARM** = hyperacute injury marker; **FLAIR** = fluid-attenuated inversion recovery; **HARM** = hyperintense acute injury marker; **ICH** = intracerebral hemorrhage; **IVH** = intraventricular hemorrhage.

Intracerebral hemorrhage (ICH) is a devastating disease often associated with poor prognosis and high mortality rates.¹ Tissue injury from primary ICH is due not only to the space-occupying effects of the initial hematoma, but also to an ongoing cascade of events resulting in toxicity from blood breakdown products, and release of thrombin and other inflammatory factors.² These events lead to blood–brain barrier (BBB) and blood–CSF barrier (BCSFB) disruption followed by development of vasogenic edema.³

Prior imaging-based studies have described perihematomal and intrahematomal postcontrast enhancement in primary ICH and its importance as a marker of poor outcome. In the MRI literature, patterns of hematoma enhancement (representing classic BBB disruption) on postcontrast T1-weighted imaging in hyperacute primary ICH have been described, including their association with hematoma expansion and outcome.⁴

Another type of contrast extravasation reported in ischemic stroke has been termed hyperintense acute injury marker (HARM), defined as the radiologic finding of hyperintense signal

Supplemental data at
www.neurology.org

Supplemental Data

From the Department of Neurology and Stroke Center (C.S.K., R.B., R.M.), Georgetown University, Washington, DC; and National Institute of Neurological Disorders and Stroke (S.W., L.L.L.), National Institutes of Health, Bethesda, MD.

Study funding: Supported in part by the Division of Intramural Research, National Institute of Neurological Disorders and Stroke (NINDS).

Disclosure: Author disclosures are provided at the end of the article.

Table 1 Patient characteristics

	All (n = 46)	HARM 0-2 (n = 23)	HARM 3-4 (n = 23)	p Value
Age, mean	65	67	64	0.41
Sex, % female	60	52	70	0.23
Baseline NIHSS, mean (median)	9 (7)	7 (5)	12 (8)	0.07
Mean arterial pressure	125	122	129	0.30
Admission glucose, mean	138	134	142	0.65
Hypertension, %	85	83	87	1.0
Diabetes, %	15	13	17	1.0
Hyperlipidemia, %	15	22	9	0.41
Tobacco use, %	17	22	13	0.70
Time from onset to MRI, median hours (range)	11:01 (0:45-81:17)	17:53 (0:52-81:17)	8:23 (0:45-36:59)	0.14
Mean ICH volume, cc	12.2	9	15	0.09
Lobar ICH location, %	22	13	30	0.28
IVH, %	17	13	22	0.44
Moderate to severe leukoaraiosis, %	57	61	52	0.55
Presence of one or more microbleeds, %	37	35	39	0.76

Abbreviations: HARM = hyperacute injury marker; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; NIHSS = NIH Stroke Scale.

within the CSF spaces visualized on postcontrast fluid-attenuated inversion recovery (FLAIR) sequences.⁵ This finding is visually distinct from and anatomically noncontiguous with the intraparenchymal enhancement seen on T1-weighted images. It has been hypothesized that HARM represents contrast leakage into the CSF space due to BCSFB or BBB disruption.⁶ In ischemic stroke, HARM is associated with severe stroke at onset, poor clinical outcome, reperfusion injury, and hemorrhagic transformation.^{5,7} The objective of this exploratory study was to characterize HARM in primary ICH, which has not been previously reported.

METHODS We performed a retrospective, cohort analysis of patients admitted to 2 hospitals with a diagnosis of primary ICH from February 2005 to April 2007. A combined total of approximately 150–175 primary ICHs are seen annually at these hospitals. Patients were included if a postgadolinium FLAIR sequence was performed within 5 days of onset. Patients were excluded if they had isolated intraventricular hemorrhage (IVH), evidence of subarachnoid blood (on CT or MRI), or warfarin-related hemorrhage.

MRIs were acquired on either 1.5 T or 3 T systems with a standardized imaging protocol designed to assure image parity across scanners. Sequences included diffusion-weighted imaging (DWI), precontrast and postcontrast FLAIR, T2*-weighted gradient echo (GRE), and contrast-enhanced perfusion imaging (fixed gadolinium dose). In the majority of cases, a precontrast and postcontrast T1-weighted image was acquired.

The precontrast and postcontrast FLAIR sequences were evaluated for the presence of HARM (without corresponding

hypointense signal on GRE) by a single reader (C.S.K.) blinded to clinical information. The presence of HARM was rated on a 5-point scale (none to bilateral and diffuse, table e-1 on the *Neurology*[®] Web site at www.neurology.org). The postcontrast T1-weighted scans were evaluated for the presence of perihematomal and intrahematomal enhancement.⁸

Standard protocol approvals, registrations, and patient consents. The study was approved by the local institutional review boards.

Statistical analysis. Group differences were analyzed using χ^2 analysis, Fisher exact test, Student *t* test, or the Mann-Whitney *U* test as appropriate. Multiple logistic regression analysis was performed to determine the effects of MRI timing and contrast dosing on HARM severity. As this was an exploratory analysis, no sample size calculation was performed. All statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS, Chicago, IL).

RESULTS A total of 46 patients met inclusion/exclusion criteria. Baseline characteristics are provided in table 1. Overall, 85% of patients showed some degree of HARM, and 50% showed moderate to severe HARM (figure 1). In all cases, the sulcal enhancement was noncontiguous with the hematoma. Table 1 also provides baseline characteristics for patients with absent or mild HARM (score 0–2) compared to those with moderate to severe HARM (score 3–4). There were no significant differences between the groups, although the moderate to severe HARM group tended to have a higher baseline NIHSS ($p = 0.07$) and larger hemorrhage volumes ($p = 0.09$). Figure 2 and figures e-1 and e-2 provide case illustrations.

Figure 1 Frequency of hyperacute injury marker (HARM) by severity across subjects

Dark gray represents the proportion of patients with less than 12 hours between last known well time and MRI, while light gray represents the proportion of patients scanned beyond 12 hours from symptom onset.

The majority of patients (67%) received the same number of gadolinium doses during the index scan. However, 10 patients had an MRI with gadolinium prior to the index scan, with the total number of doses ranging from 1 to 4. Table e-2 shows the group characteristics of the subset of patients without a prior MRI. HARM severity tended to decrease with greater elapsed time between symptom onset and MRI ($r = -0.34$, $p = 0.02$), whereas HARM severity increased with higher number of gadolinium doses ($r = 0.38$, $p = 0.01$). On logistic regression analysis, independent predictors of HARM severity included higher number of gadolinium doses ($B = 0.77$, $p = 0.025$) with a trend for shorter time interval to MRI ($B = -0.02$, $p = 0.057$).

Of the 32 patients with postcontrast T1-weighted imaging, 72% had at least one type of enhancement, 19 with perihematomal (rim) and 10 with intrahematomal (spot sign) enhancement. Ninety-six percent of patients with enhancement also had HARM. Among patients without enhancement on postcontrast T1, all patients had HARM. See figures e-2 and e-3 for examples.

DISCUSSION This retrospective analysis characterizes the previously unreported finding of HARM in primary ICH. In our cohort, HARM was visualized in 85% of patients and was remote from the hematoma in all cases. In one-half of patients, HARM was graded as moderate to severe. Intraparenchymal enhancement on T1-weighted imaging was visualized in approximately 3-quarters of patients (either at the rim of the hematoma or within the core [MRI equivalent of the spot sign⁸]). Visual inspection demonstrated that HARM and T1 enhancement can occur independently, and an emerging literature suggests that these are 2 distinct pathophysiologic phenomena.

A growing body of data has elucidated the time course and cascade of events that lead to brain injury and CNS barrier disruption following ICH.^{1,2} An early phase of CNS barrier opening likely occurs in the first few hours after ICH, followed later by frank BBB and BCSFB permeability due to release of oxygen free radicals, matrix metalloproteinases, and other factors. It is generally accepted that contrast extravasation within or at the rim of the hematoma represents classic BBB disruption (particularly in the form of the spot sign) and is a marker for hematoma expansion and poor outcome.⁸ These forms of local

Figure 2 Example of development of multipunctate contrast enhancement

(A) Right frontal lobar hematoma. (B) Precontrast fluid-attenuated inversion recovery (FLAIR) sequence. (C) Interval development of punctuate regions of contrast enhancement in the sulci bilaterally (arrows). GRE = gradient echo.

enhancement on T1-weighted sequences are likely due to direct contrast leakage from ruptured vessels (spot sign), or microscopic disruption of the BBB in perihematoma regions (rim enhancement). In contrast, the pathophysiology leading to HARM (FLAIR sulcal enhancement remote from the hematoma) is less well understood, particularly in ICH, but likely involves a combination of BBB and BCSFB disruption.

As an imaging indication of CNS barrier disruption, HARM is an appealing biomarker (analogous to, but distinct from, the spot sign) for testing putative therapies for ICH aimed at stabilizing CNS barriers.^{9,10} Since studies have demonstrated that development of CNS barrier permeability precedes development of vasogenic edema, therapeutic agents that specifically target CNS barrier disruption have the potential to reduce mass effect and interrupt the further cascade of injury.

The study has a number of limitations. The sample may be biased, as included subjects had relatively small hematoma volumes and low NIHSS scores, likely due to MRI eligibility criteria. Although unlikely, GRE may not have completely excluded a component of subarachnoid blood appearing as HARM. While variable gadolinium dosing between patients was a limitation, it did allow us to demonstrate that higher number of doses were correlated with higher HARM scores. Due to small sample size, we were only able to identify a trend toward an association between HARM severity and 1) higher NIHSS scores, 2) larger hematoma volumes, and 3) shorter time to MRI. Further studies employing larger datasets are needed to confirm these findings, define the time course of HARM, and elucidate its prognostic implications in ICH.

AUTHOR CONTRIBUTIONS

Dr. Kidwell: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; statistical analysis; study supervision or coordination; acquisition of data. Dr. Burgess: drafting/revising the manuscript for content, including medical writing for content; analysis or interpretation of data; acquisition of data. Dr. Menon: drafting/revising the manuscript for content, including medical writing for content; analysis or interpretation of data; acquisition of data. Dr. Warach: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; acquisition of data; obtaining funding. Dr. Latour: drafting/revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; acquisition of data.

ACKNOWLEDGMENT

The authors thank the NIH Stroke Natural History Investigators.

DISCLOSURE

Dr. Kidwell serves on the editorial boards of *Neurocritical Care*, the *Journal of Neuroimaging*, and *Stroke Research and Treatment*; serves/served as a consultant for Embrella Cardiovascular, Inc., Inc. and Simcere Pharmaceutical Group; and receives research support from Baxter International Inc. and the NIH/NINDS. Dr. Burgess receives research support from the NIH/NINDS. Dr. Menon receives research support from the NIH (NINDS, NIMHD). Dr. Warach serves on the editorial boards of the *Journal of Cerebral Blood Flow and Metabolism*, *Stroke*, *The Lancet Neurology*, *International Journal of Stroke*, and *Cerebrovascular Diseases*; and receives research support from NINDS, Division of Intramural Research. Dr. Latour reports no disclosures.

Received April 6, 2011. Accepted in final form August 3, 2011.

REFERENCES

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet* 2009;373:1632–1644.
2. Xi G, Keep RF, Hoff JT. Mechanisms of brain injury after intracerebral haemorrhage. *Lancet Neurol* 2006;5:53–63.
3. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis* 2010;37:13–25.
4. Murai Y, Ikeda Y, Teramoto A, Tsuji Y. Magnetic resonance imaging-documented extravasation as an indicator of acute hypertensive intracerebral hemorrhage. *J Neurosurg* 1998;88:650–655.
5. Latour LL, Kang DW, Ezzeddine MA, Chalela JA, Warach S. Early blood-brain barrier disruption in human focal brain ischemia. *Ann Neurol* 2004;56:468–477.
6. Henning EC, Latour LL, Warach S. Verification of enhancement of the CSF space, not parenchyma, in acute stroke patients with early blood-brain barrier disruption. *J Cereb Blood Flow Metab* 2008;28:882–886.
7. Kidwell CS, Latour L, Saver JL, et al. Thrombolytic toxicity: blood brain barrier disruption in human ischemic stroke. *Cerebrovasc Dis* 2008;25:338–343.
8. Goldstein JN, Fazen LE, Snider R, et al. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology* 2007;68:889–894.
9. Belayev L, Saul I, Busto R, et al. Albumin treatment reduces neurological deficit and protects blood-brain barrier integrity after acute intracortical hematoma in the rat. *Stroke* 2005;36:326–331.
10. Sood RR, Taheri S, Candelario-Jalil E, Estrada EY, Rosenberg GA. Early beneficial effect of matrix metalloproteinase inhibition on blood-brain barrier permeability as measured by magnetic resonance imaging countered by impaired long-term recovery after stroke in rat brain. *J Cereb Blood Flow Metab* 2008;28:431–438.

The Cure Is in Your Hands

Hardships caused by neurologic disorders affect **ONE IN SIX** Americans. The cure is in your hands.

Support research and education to cure brain disorders.

www.aan.com/foundation