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ORIGINAL ARTICLE

Brain Injury Visible on Early MRI After Subarachnoid Hemorrhage Might Predict Neurological Impairment and Functional Outcome

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Abstract
Background In subarachnoid hemorrhage (SAH), brain injury visible within 48 h of onset may impact on admission neurological disability and 3-month functional outcome. With volumetric MRI, we measured the volume of brain injury visible after SAH, and assessed the association with admission clinical grade and 3-month functional outcome.
Methods Retrospective cohort study conducted in the Neurocritical Care Division, Columbia University Medical Center, New York, USA. On brain MRI acquired within 48 h of SAH-onset and before aneurysm-securing ($n = 27$), two blinded readers measured DWI and FLAIR-lesion volumes using semi-automated, computer segmentation software.
Results Compared to post-resuscitation Hunt–Hess grade 1–3 (70 %), high-grade patients (30 %) had higher lesion volumes on DWI (34 ml [IQR: 0–64] vs. 2 ml [IQR: 0.5–7], $P = 0.02$) and on FLAIR (81 ml [IQR: 24–127] vs. 3 ml [IQR: 0–27], $P = 0.02$). On DWI, each 10 ml increase in lesion volume was associated with a 101 %-increase in the odds of presenting with 1 grade more in the Hunt–Hess scale (aOR 2.01, 95 % CI 1.10–3.68, $P = 0.02$), but was not significantly associated with 3-month outcome. On FLAIR, each 10 ml increase in lesion volume was associated with 34 % higher odds of a 1-point increase on the Hunt–Hess scale (aOR 1.34, 95 % CI 1.06–1.68, $P = 0.01$) and 139 % higher odds of a 1-point increase on the 3-month mRS (aOR 2.39, 95 % CI 1.13–5.07, $P = 0.02$).
Conclusion The volume of brain injury visible on DWI and FLAIR within 48 h after SAH is proportional to neurological impairment on admission. Moreover, FLAIR-imaging implicates chronic brain injury—predating SAH—as potentially relevant cause of poor functional outcome.

Keywords Subarachnoid hemorrhage · Brain injury · MRI · Biomarker · Neurological disability · Outcome

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Introduction

Early after onset of subarachnoid hemorrhage (SAH), brain injury is visible on magnetic resonance imaging (MRI). Part of brain injury is acute; the rest is chronic, predating SAH. Acute brain injury results from a collection of pathological processes that directly affect the brain parenchyma and microvasculature at SAH-onset, including

ictal ischemic injury. Ictal ischemic injury is visible, on computed tomography (CT), in 7 % of Hunt–Hess grade 4 or 5 patients as evidenced by acute infarction within 48 h of SAH-onset, but this may represent the "tip of the iceberg" [1]. On diffusion-weighted imaging (DWI) acquired within 96 h from SAH-onset, focal or symmetric bilateral ischemic injury is visible in up to 86 % of Hunt–Hess grade 4 or 5 patients [2, 3]. While the lesions with signal increase on DWI and decrease on ADC are acute, DWI misses some acute injury (e.g., periventricular, transependymal edema) and chronic lesions. This type of injury is better visible on fluid-attenuated inversion recovery (FLAIR) imaging. From acute ischemic stroke, we know that both the volumes of acute and chronic lesions are associated with outcome 3 months after stroke [4, 5]. In SAH, it remains unknown whether the volume of injury on DWI and FLAIR—after adjustment for neurologic impairment on admission and age—is associated with outcome at 3 months. In this study, with MR-volumetry, we measured the volume of injury visible on DWI and FLAIR acquired within 48 h from SAH-onset and before aneurysm-securing. We then sought to determine the association between the volumes of injury and outcome at 3 months, adjusted for neurological impairment on admission.

Methods

Ethics Statement

This study was conducted according to the principles expressed in the Declaration of Helsinki and approved by the Institutional Review Board. All patients or their welfare guardians provided written informed consent for the collection of data, blood samples, and subsequent analyses.

Subjects

All patients with a spontaneous SAH admitted to the Columbia University Medical Center Neurological Intensive Care Unit between July 1996 and July 2012 were offered enrollment into the Columbia University SAH Outcomes Project, a prospective cohort study designed to identify novel risk factors for poor outcome. Patients who underwent a brain MRI within 48 h of SAH-onset and before aneurysm-securing were included in the current analysis. Five of the enrolled patients (19 %) were included in a prior publication documenting the phenomenon of acute DWI injury in poor-grade SAH (without volumetry and outcome assessment) [2]. All of the MRI scans were obtained for clinical purposes, as deemed indicated by the attending physician on call. The most frequent indication was detection of a thrombosed aneurysm that was initially occult on angiography.

Clinical Definitions

Severity of admission neurological grade was assessed using the Hunt–Hess scales and World Federation of Neurological Surgeons SAH grading scale, both assessed after resuscitation [6, 7]. By convention, we used the Hunt–Hess scale as the primary instrument for grading neurological impairment, with grades 1, 2, and 3 classified as good grade and grades 4 and 5 (stupor and coma, respectively) as poor grade. CT scans were evaluated by study neurointensivists for extent of initial bleeding using the modified Fisher scale (mFS) [8], Hijdra SAH score [9], intraventricular hemorrhage score [10], and volume of space-occupying subarachnoid or intraparenchymal clot using the ABC/2 method [11]. Hydrocephalus was classified as present or absent based on the bicaudate index according to the upper limit of normal for decile of age [12]. On CT, global cerebral edema (GCE) was assessed based on the published diagnostic criteria [13]. Medical and surgical managements were otherwise performed as previously described [14].

MR Techniques

All MRI were obtained within 48 h from SAH-onset, on a 1.5 or 3.0 T MRI system (Signa, GE Healthcare) using an 8-channel head array coil (Signa HDxt, GE Healthcare). DWI used a single shot, spin echo, echo planar sequence with TR 7,000 ms/TE 73 ms; FOV 220 mm; 128 × 192 matrix; slice thickness 5 mm with no gap; bandwidth 1,953 Hz/pixel; with P values of 0 and 1,000 s/mm^2. Apparent diffusion coefficients (ADC) maps were generated in Functool (GE Medical Systems, Milwaukee, Wisconsin). Axial FLAIR was performed with TR 9,500 ms/TE 127 ms; TI 2,250 ms; slice thickness 5 mm with no gap; FOV 225 mm. A T1-weighted 3D IR-FSPGR sequence was obtained with TI 450 ms; TR 10.2 ms; TE 4.2 ms; α 13°; FOV 250 mm; matrix 256 × 256; no contrast medium; slice thickness 1.2 mm. Total scan time was approximately 4 min 15 s.

Computed-Aided Volumetry (CAV)

The algorithm for CAV involves the reader manually selecting a region-of-interest (ROI) that roughly encloses the area of injured brain on a single image [15]. The algorithm then automatically localizes the boundaries of injured brain, excluding surrounding non-injured brain

tissue. Once the segmentation is completed on an image, the injury contour is propagated to its neighboring images, serving as an initial ROI for subsequent segmentations on the neighboring images. The process continues iteratively until brain injury on all images is segmented. To ensure correct results, computer-generated injury contours are superimposed onto the original images for inspection and manual modification. Once the segmentation is ended, the injury volume was automatically calculated (see Video as supplementary material). The CAV algorithm, along with manual functions to select ROI and modify suboptimal contours, has been integrated into a user-friendly image viewing software developed with MATLAB Version 7.8 (Natick, Massachusetts) by the Computational Imaging Laboratory at the Columbia University College of Physicians and Surgeons (Guo X, Zhao B, Schwartz L. A Method and apparatus for computer-aided tumor and organ segmentation. Columbia University Invention Report # CU12260).

MR Interpretation

Prior to their reading, all MRI were de-identified to blind the two readers to all clinical and outcome characteristics. A board-certified neurologist (GMDM) performed the CAV on the DWI and FLAIR images. A board-certified neuroradiologist (CGF) then checked the CAV measurements on DWI and FLAIR, and adjusted them as needed. On DWI, the two readers contoured hyperintense lesions only with corresponding low signal on ADC, this to avoid measuring of T2 shine-through. On FLAIR, since it was impossible for the blinded readers to determine the age of these lesions, all hyperintense regions were contoured. On T1, the whole brain surface and ventricles were contoured to compute the volume of the whole brain parenchyma and the volume of the brain ventricles. In cases of discrepancy between readers regarding injured brain, images were re-reviewed together to reach a consensus.

Outcomes Assessment

At 3 months, trained personnel-rated outcome using the modified Rankin scale (mRs) by in-person or telephone interview [16]. Favorable functional outcome was defined as mRs of 0–3, unfavorable functional outcome as mRs of 4–6. The treating and rating teams were blinded to the measured volumes.

Statistical Analysis

Discrete variables were expressed as counts (percentages) and continuous variables as medians (interquartile range, meaning range between the first and third quartile). Frequency comparisons for categorical baseline measurements were performed by Fisher's exact test. Two-group comparison of continuous data was performed by the Mann–Whitney *U* test or two-sample *t* test. Inter-reader agreement on the volume of brain injury was computed with Lin's concordance correlation coefficient, which was developed to assess agreement on a continuous measure, and encompasses a measure of both precision and accuracy [17]. To compute the adjusted odds ratios (OR) of the volume of brain injury for increasing admission Hunt–Hess grade and 3-month mRs, we developed ordinal logistic models adjusting for established predictors of neurological disability and unfavorable outcome [18]. As statistical software, we used STATA 12.

Results

Subjects

We included 27 patients who underwent an MRI within 48 h from SAH-onset and before aneurysm-securing from October 20, 1999 through July 13, 2012. Baseline clinical characteristics are shown in Table 1. The entire spectrum of Hunt–Hess grades was represented. Intraventricular hemorrhage was present in 37 %, and space-occupying hematoma was identified in 18.5 %.

Pattern of Injury, Clinical Grade on Admission, and Volume of Brain Injury

Overall, 79 % had lesions on DWI, and 76 % of patients had lesions on FLAIR. The most common patterns of injury were both DWI- and FLAIR-positive lesions corresponding with territorial infarction or patchy injury, and symmetrical periventricular DWI-negative and FLAIR-positive lesions (Fig. 1). On DWI, median lesion volume was 4 ml (IQR: 0.3–28). The DWI-lesion volume was 18-fold higher between Hunt–Hess 4–5 patients than among grade 1–3 patients (34 ml [IQR: 0–64] vs. 2 ml [IQR: 0.5–7], $P = 0.02$). After adjusting for age, hydrocephalus, and modified Fisher score, each 10 ml increase in DWI-lesion volume was associated with an increase by 101 % in the odds of presenting with 1 grade more on the Hunt–Hess grade scale (aOR 2.01, 95 % CI 1.10–3.68, $P = 0.02$; see Table 2; Fig. 2).

On FLAIR, the median volume of early brain injury was 17 ml (IQR: 0.4–71), and the inter-reader agreement on the measured volumes was optimal (concordance correlation coefficient = 0.92). FLAIR-lesion volume was more than 25 times greater among Hunt–Hess grade 4 or 5 patients compared to grade 1–3 patients (81 ml [IQR: 24–127] vs.

Table 1 Values are *n* (%) or median (interquartile range)

Patient characteristics	Total $n = 27$	
Age, years	55.0	(45.0–74.0)
Women (%)	16	(59.3)
Non-White race/ethnicity, *n* (%)	16	(59.3)
Hunt–Hess grade, *n* (%)		
1, Mild headache	10	(37.0)
2, Severe headache	5	(18.5)
3, Lethargy, confusion, mild focal deficits	4	(14.8)
4, Stupor	4	(14.8)
5, Coma	4	(14.8)
Modified Fisher grade, *n* (%)		
1, No thick cisternal blood, −IVH	10	(37.0)
2, No thick cisternal blood, +IVH	3	(11.1)
3, Thick cisternal blood, −IVH	7	(25.9)
4, Thick cisternal blood, +IVH	7	(25.9)
Hydrocephalus	7	(25.9)
Intracerebral clot	5	(18.5)
Intracerebral clot volume (ml)	11.5	(1–32)
IVH sum score[a]	0	(0–3)
Hijdra SAH sum score[b]	11	(4–22)
APACHE-II score[c]	6	(6–19)

Because of rounding, percentages may not total 100. IVH denotes intraventricular hemorrhage

[a] Range: 0, no IVH; 12, all ventricles completely filled with IVH

[b] Range, 0 = no blood, 30 = complete filling of all cisterns and fissures

[c] Acute physiology and chronic health evaluation II. Range, 0–71. Higher scores indicate more sever disease

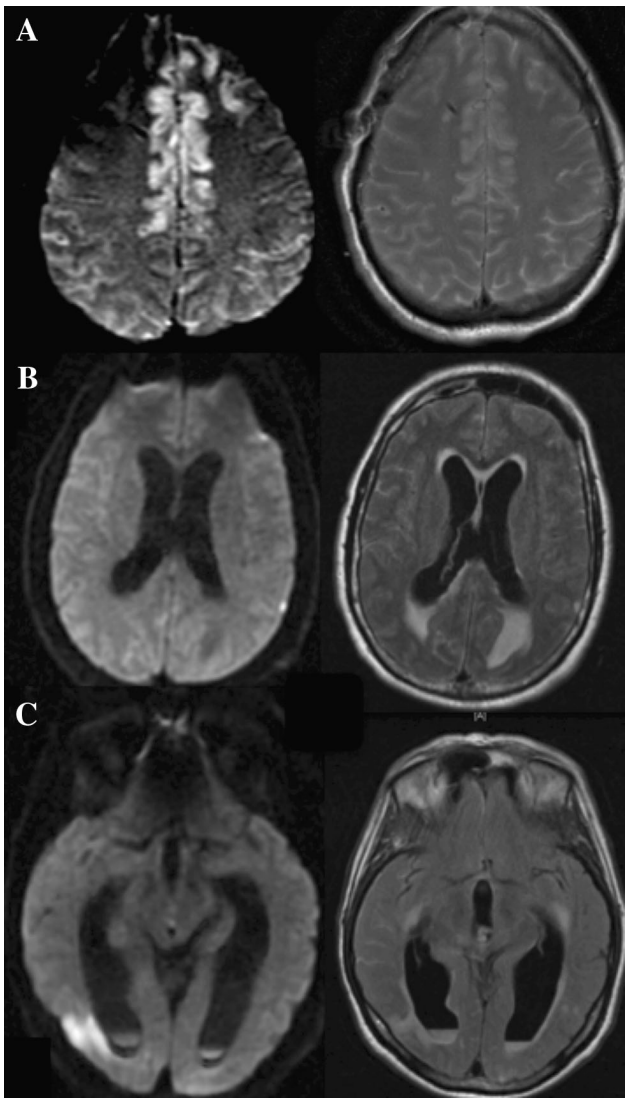

Fig. 1 Common patterns of brain injury. **a** displays bilateral injury to anterior cerebral artery territories visible on both diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR); **b** displays hydrocephalus and periventricular injury on FLAIR but not on DWI, and displays a punctate DWI lesion in the left parietal cortex; **c** displays patchy injury to the right temporo-occipital junction on both DWI and FLAIR

3 ml [IQR: 0–27], $P = 0.02$). After adjusting for age, hydrocephalus, and modified Fisher score, for each increase in volume by 10 ml, the odds of a 1-grade increase in admission Hunt–Hess grade increased by 34 %, (aOR 1.34, 95 % CI 1.06–1.68, $P = 0.01$; see Fig. 2; Table 2). Replacing the Hunt–Hess scale with the WFNS scale did not alter the statistical significance of these observations.

Three-Month Outcome and Volume of Early Brain Injury

At 3 months after SAH, 71 % of patients were mRs 0–3, indicating the ability to ambulate independently, 5 % were mRS 4–5, indicating that they were unable to ambulate independently or bedbound, and 24 % had died. DWI-lesion volumes were 40 times higher in patients with mRs 4–6 versus mRs 0–3 (41 ml [IQR: 9–60] vs. 1 ml [IQR: 0.1–3], $P = 0.04$), see Fig. 1. However—after adjusting for age, Hunt–Hess grade, and modified Fisher score—DWI-lesion volume was not significantly associated with mRs scores at 3 months. FLAIR-lesion volumes were more than 40 times higher in patients with mRs 4–6 versus mRs 0–3 (87 ml [IQR: 33–151] vs. 2 ml [IQR: 0–17], $P = 0.002$). After adjusting for age, Hunt–Hess grade, and modified Fisher score, each 10 ml increase in FLAIR-lesion volume was associated with a 139 % increase in the odds of a 1-point increase on the mRs (aOR 2.39, 95 % CI 1.13–5.07, $P = 0.02$; see Table 2; Fig. 3). Replacing the Hunt–Hess with the WFNS scale did not modify the associations between functional outcome and DWI-or FLAIR-lesion volume.

Table 2 OR denotes odds ratio

Neurological disability on admission: multivariate logistic models					
All OR refer to an increase of 1 point in the Hunt & Hess score on admission					
	Adjusted OR	95 % Confidence interval			*P* value
Model 1: DWI-volume as main predictor					
DWI, any increase by 10-ml	2.01	1.10	–	3.68	0.02
Age, per year	0.98	0.91	–	1.05	0.57
Hydrocephalus	3.27	0.43	–	24.79	0.25
Modified Fisher score, per grade increase	3.54	1.19	–	10.56	0.02
Model 2: FLAIR-volume as main predictor					
FLAIR, any increase by 10-ml	1.34	1.06	–	1.68	0.01
Age, per year	0.99	0.93	–	1.05	0.67
Hydrocephalus	2.56	0.34	–	19.21	0.36
Modified Fisher score, per grade increase	2.35	1.04	–	5.28	0.04
Outcome at 3 months. ordinal logistic models					
All OR refer to an increase of 1 point in the modified Rankin score					
	Adjusted OR	95 % Confidence interval			*P* value
Model 3: DWI-volume as main predictor					
DWI, any increase by 10-ml	2.39	0.12	–	49.5	0.57
Age, per year	1.09	0.98	–	1.22	0.12
Hunt–Hess 4–5 vs. 1–3	3.42	0.80	–	14.56	0.10
Modified Fisher score, per grade increase	0.40	0.06	–	2.72	0.35
Model 4: FLAIR-volume as main predictor					
FLAIR, any increase by 10-ml	2.39	1.13	–	5.07	0.02
Age, per year	1.03	0.97	–	1.11	0.34
Hunt–Hess, per grade	3.05	0.94	–	9.92	0.06
Modified Fisher score, per grade increase	0.74	0.26	–	2.09	0.57

Hydrocephalus was classified as present or absent based on the bicaudate index according to the upper limit of normal for decile of age

Clinical Variables Associated with Brain Injury

Ictal loss of consciousness occurred in 27 % of patients. Among patients with ictal loss of consciousness, volumes of brain injury were significantly higher on FLAIR (71 ml [IQR, 35–96] vs. 16 ml [IQR, 0.4–43], $P = 0.04$), but not on DWI sequences (11 ml [IQR, 0–60] vs. 0.8 ml [IQR, 0.3–6.1], $P = 0.22$). Among patients with GCE (19 %), volumes of brain injury on DWI and FLAIR were not significantly higher compared to patients without GCE. Similarly, brain volume, used as a surrogate marker of GCE, was not associated with brain injury on both DWI and FLAIR (data not shown). Hydrocephalus, as assessed by bicaudate index and ventricular volume, was also not associated with volume of brain injury on DWI or FLAIR. Four patients (15 %) showed one or more injuries on either DWI or FLAIR in the brainstem or thalamus, and 50 % of these patients presented with a Hunt–Hess grade of 4–5 compared to 26 % of patients with no injury in the brainstem or thalamus ($P = 0.6$).

Discussion

In this study of SAH patients who underwent MRI imaging within 48 h of onset and before aneurysm-securing, we found a significantly increased volume of brain injury on DWI and on FLAIR in poor grade compared to good-grade patients. FLAIR-lesion volume, but not DWI, was also associated with 3-month functional outcome. These findings confirm that SAH involves not only bleeding but also direct tissue injury, and that MRI can be used to measure this injury. Further studies are needed to confirm the prognostic value of brain MRI in SAH, and elucidate the mechanisms that lead to tissue injury. Our study population included a broad spectrum of admission Hunt–Hess grades

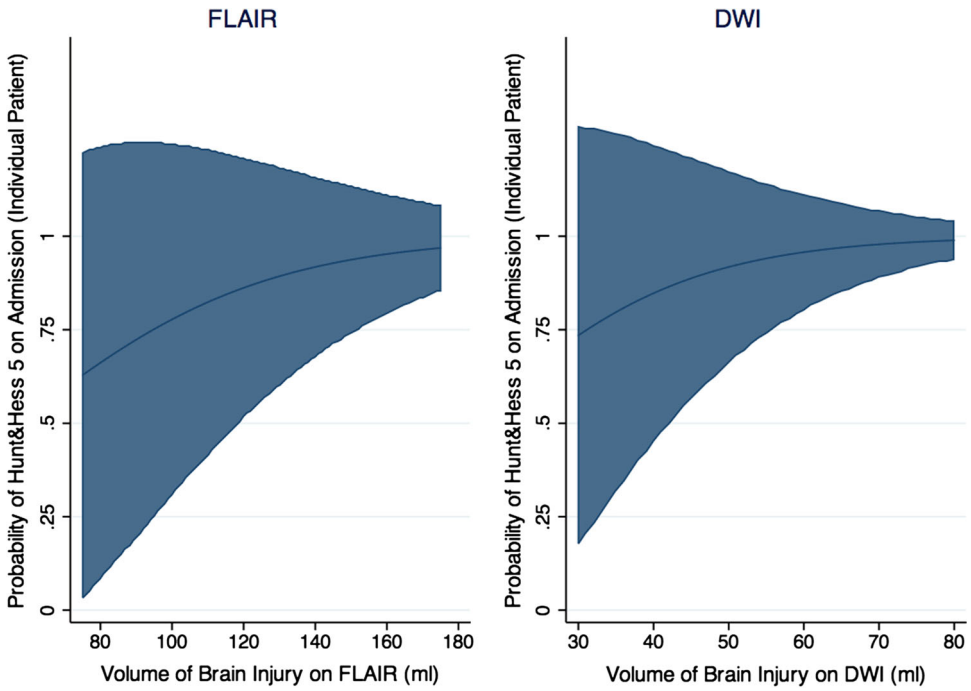

Fig. 2 Adjusted estimated probability of being admitted with a Hunt–Hess of 5 relative to the volume of brain injury on DWI and FLAIR for a 55-years-old patient with a modified Fisher score of 4, and with hydrocephalus on CT. The *shaded areas* represent the 95 % confidence interval of the estimated probability. The plot was generated from the fitted logistic regression model, with—as outcome—Hunt–Hess of 5, and—as covariates—age, high-grade modified Fisher score, and hydrocephalus on CT

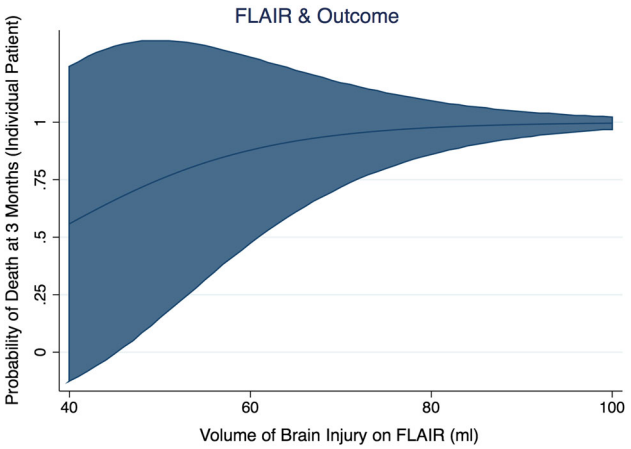

Fig. 3 Adjusted estimated probability of death at 3 months relative to the volume of brain injury on FLAIR for a 70-years-old patient, with a Hunt–Hess of 3, and a modified Fisher score of 4. The *shaded areas* represent the 95 % confidence interval of the estimated probability. The plot was generated from the fitted logistic regression model, with a mRs of 6 as outcome, and—as covariates—age, Hunt–Hess grade on admission, and modified Fisher score

that is similar to the SAH patient population at large. The 79 % frequency of DWI injury in our study confirms the findings of two prior studies that found similar findings in 71 and 86 % of poor-grade patients [2, 3]. Our findings build on these observations by showing that DWI-positive injury occurs in both good and poor-grade patients, with poor-grade patients suffering from a substantially greater lesion volume. Since we contoured DWI-injuries only with low signal on ADC—making T2 shine-through unlikely—DWI likely highlighted regions of cytotoxic edema. Cytotoxic edema can stem from hypoperfusion due to reduced cerebral perfusion from increased intracranial pressure. Alternative mechanisms leading to cytotoxic edema are ultra-early vasospasm and local vessel thrombosis [19]. The pattern of isolated punctate DWI injury found in some of our good-grade patients (Fig. 1b) resembles a similar pattern recently described in acute intracerebral hemorrhage [20].

In contrast to DWI, FLAIR displays chronic brain injury, but may also display acute injury not captured by DWI—e.g., periventricular, transependymal edema. As our blinded readers were unable to differentiate chronic from acute lesions on FLAIR—and did not attempt to do so—injury volume on FLAIR represents a combination of largely chronic and some acute injury. Of note, lesion volume on FLAIR, but not on DWI, was associated with functional outcome at 3 months after adjusting for predictors of outcome including Hunt–Hess grade and age. This finding mirrors one in ischemic stroke, where—after adjusting for age—higher volumes of chronic white matter injury are associated with unfavorable outcomes at 3–6 months. As Kissela et al. [4, 5] discussed, recovery in patients with premorbid white matter injury may be limited due to reduced neuroplasticity from damage to the white matter tracts [4]. After adjusting for the volume of brain injury on FLAIR, age was not significantly associated with outcome. This finding may point to chronic brain injury mediating the effect of higher age on unfavorable outcome after SAH (higher age → chronic brain injury → reduced neuroplasticity/recovery → unfavorable outcome after SAH).

Concerning acute FLAIR-injury, periventricular FLAIR-positive, and DWI-negative lesions (Fig. 1b) may suggest acute hydrocephalus as mechanism of injury. However, we were unable to demonstrate an association between injury volume on FLAIR and bicaudate index or need for EVD, suggesting that causes other than hydrocephalus may play a role as well. Other potential candidates for acute white matter injury in SAH that deserve further study are hemotoxicity related to intraventricular blood, axonal injury, and white matter pathway damage. As biomarker for white matter injury, neurofilaments, released in the blood and cerebrospinal fluid, may be a useful to constantly monitor the dynamics and response to therapy of white matter injury following SAH [21].

We explored several candidate variables that might exacerbate or correlate with the extent of brain injury after SAH, and found significant associations with ictal loss of consciousness. Ictal loss of consciousness was associated with larger volumes of brain injury on DWI and FLAIR, but only on FLAIR, the volumes were significantly larger. While ictal loss of consciousness likely results from a brief period of intracranial circulatory hypoperfusion, chronic brain injury seen on FLAIR may point to a reduced ability of the brain of maintaining consciousness at SAH-onset.

Although loss of consciousness at SAH-onset has also been implicated as a risk factor for GCE, a predictor of poor outcome, we were unable to identify any relationship between the extent of DWI- and FLAIR-lesion volume and the CT appearance of GCE, or increased whole-brain volume measured on concurrent T1 images.

Despite being the first study to assess the link between quantified brain injury on DWI and FLAIR and outcome after SAH, this study has limitations. First, FLAIR-lesion volumes certainly included mostly chronic injury, but we speculate that brain injury predating SAH matters by contributing to the poor outcomes after SAH. Second, the retrospective design did not allow us to assess the evolution of brain injury over time. Third, the relatively small study sample of 27 patients limited statistical power to look more in detail at the impact of injury location on neurological disability and outcome, and may have been subject to selection bias that comes with any study of a convenience sample. Moreover, all patients underwent MRI for clinical reasons, introducing a possible bias. For instance, thrombosed aneurysms may be linked to high-grade SAH. Alternatively, more patients with preexisting infarcts or white matter disease might have been more likely to get an MRI. The small sample size results from the strict inclusion criteria (MRI within 48 h from SAH-onset, but before aneurysm-securing). Finally, the 5 mm slice thickness used in our clinical MR-imaging protocol further prevented us from allocating volumes of injury to precise neuroanatomical structures. In conclusion, volumetry on DWI and FLAIR establishes that brain injury visible within 48 h after SAH is proportional to neurological impairment on admission. Moreover, FLAIR-imaging implicates chronic brain injury—predating SAH—as potentially relevant cause of poor functional outcome.

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