Subarachnoid Extension of Primary Intracerebral Hemorrhage is Associated With Poor Outcomes

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Background and Purpose—Extension of hemorrhage into the subarachnoid space is observed in primary intracerebral hemorrhage (ICH), yet the phenomenon has undergone limited study and is of unknown significance. The objective of this study is to evaluate the incidence, characteristics, and clinical consequences of subarachnoid hemorrhage extension (SAHE) in ICH on functional outcomes.

Methods—Patients with primary ICH were enrolled into a prospective registry between December 2006 and June 2012. Patients were managed and serial neuroimaging was obtained per a structured protocol. Presence of any subarachnoid blood on imaging was identified as SAHE by expert reviewers blinded to outcomes. Regression models were developed to test whether the occurrence of SAHE was an independent predictor of functional outcomes as measured with the modified Rankin Scale.

Results—Of 234 patients with ICH, 93 (39.7%) had SAHE. Interrater agreement for SAHE was excellent (kappa=0.991). SAHE was associated with lobar hemorrhage location (65% of SAHE vs 19% of non-SAHE cases; P<0.001) and larger hematoma volumes (median 23.8 vs 6.7; P<0.001). Fever (69.9% vs 51.1%; P=0.005) and seizures (8.6% vs 2.8%; P=0.07) were more common in patients with SAHE. SAHE was a predictor of death by day 14 (odds ratio, 4.45; 95% confidence interval, 1.88–10.53; P=0.001) and of higher (worse) modified Rankin Scale scores at 28 days (odds ratio, 1.76 per mRS point; 95% confidence interval, 1.01–3.05; P=0.012) after adjustment for ICH score.

Conclusions—SAHE is associated with worse modified Rankin Scale independent of traditional ICH severity measures. Underlying mechanisms and potential treatments of SAHE require further study. (Stroke. 2013;44:653-657.)

Key Words: cerebral hemorrhage ■ intracranial hemorrhages ■ outcome assessment ■ subarachnoid hemorrhage

The 1-year mortality rate from intracerebral hemorrhage (ICH) exceeds 50% and does not appear to be improving.1 Elucidating mechanisms of injury in ICH is crucial for developing prognostic tools and therapeutic interventions. Injury from the parenchymal hematoma is obviously important, yet associations reported between intraventricular and subdural hemorrhage extension and worse outcome suggest secondary mechanisms distinct from the intraparenchymal pathology.2,3

Subarachnoid extension of hemorrhage (SAHE) has not been systematically studied as a possible contributor to functional outcomes in patients with primary ICH. Deposition of blood products in the subarachnoid space after aneurysm rupture triggers numerous pathological processes leading to cortical dysfunction, injury, and disability, yet it is uncertain whether the quantity of subarachnoid blood seen in some cases of ICH contributes meaningfully to brain injury.4,5 We sought to test the hypothesis that SAHE, radiographic extension of hemorrhage into the subarachnoid space after ICH, is independently associated with worse outcomes in patients with primary ICH.

Methods

Patients presenting to Northwestern Memorial Hospital with ICH between December 2006 and June 2012 were prospectively enrolled in an observational cohort study. All cases were diagnosed by a board-certified vascular neurologist or neurointensivist using computed tomography (CT) or magnetic resonance imaging (MRI). Patients with ICH attributed to trauma, hemorrhagic conversion of ischemic stroke, subdural hemorrhage extension and worse outcome suggest secondary mechanisms distinct from the intraparenchymal pathology.2,3

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Demographic information, medical history, medication history, standardized clinical instruments (Glasgow Coma Scale, National Institutes of Health Stroke Scale, pre-ICH modified Rankin Scale [mRS]), pretreatment blood pressure, laboratory data, imaging data, medical management variables, surgical interventions, and medical complications were prospectively recorded. A certified examiner recorded the National Institutes of Health Stroke Scale and mRS at 14 days or discharge, whichever came first. The mRS also was recorded prospectively at 28 days and at 3 months with a validated questionnaire.6

Each neuroimaging study obtained during the initial hospitalization was reviewed by a board-certified neuroradiologist (M.B.M.) and board-certified neuroradiologist (A.J.N.) to identify the appearance of subarachnoid blood while blinded to patient outcomes. Interrater reliability was evaluated by kappa coefficient. Hematoma volumes were measured on industry-standard DICOM images from both referring hospitals and ours using Analyze software (Mayo Clinic, Rochester, MN) with a semiautomated process, a technique with high reliability that has been used as an end point in other ICH studies, as we have previously described.6

Student t test (for normally distributed data), Fisher exact test (for categorical variables), and Mann–Whitney U test (for non-normally distributed data) were used to compare characteristics of subjects with and without SAHE. The primary analysis tested whether SAHE was associated with the mRS after adjustment for the ICH score.9 A binary logistic regression model was used to test for death within the first 14 days, and an ordinal regression model was used to test SAHE and ICH score with functional outcome measured by mRS at 28 days and at 3 months. The ICH score has been validated as a predictor of functional outcomes at 30 days and at 3 months post-ICH.11 Ordinal regression technique was chosen for mRS analysis because of its superior sensitivity with ordinal outcome variables compared with dichotomous outcomes.12 For the ordinal logistic regression models, the proportional odds assumption was assessed with the test of parallel lines and significance was confirmed by 2-log likelihood. For the secondary analysis, demographic and initial clinical variables found to be significant (P<0.05) on the univariate analysis were entered into a logistic regression model with SAHE to test for association with death by day 14. Because of the number of variables, a stepwise backward variable removal technique was used. The purpose of the secondary analysis was exploratory to identify any other potentially relevant variables, given that we were studying a previously unexplored phenomenon. Validity of the logistic regression models was assessed with Pearson and deviance for goodness of fit. We used standard statistical software (IBM SPSS 20).

The study was approved by the Institutional Review Board. Written informed consent was obtained from the patients or their legally authorized representative. The Institutional Review Board approved a waiver of consent for patients who died during initial hospitalization or who were incapacitated and for whom a legal representative could not be located.

Results

There were 234 patients in the study cohort, of whom 93 (39.7%) had SAHE. Interrater agreement for the identification of SAHE was excellent (kappa=0.991). Of those 93 patients with SAHE, 85 (91.4%) had cases of subarachnoid blood along the convexity ipsilateral to the primary hematoma, although subarachnoid blood also was seen in the contralateral convexity (36; 38.7%), basilar cisterns (18; 19.4%), and infratentorially (13; 14.0%). Diffuse, thick subarachnoid blood was rare. Most patients had small collections of subarachnoid blood in a few sulci. Subdural blood was seen in 28 cases (12.0%) of the overall cohort.

The characteristics of the patients with and without SAHE are summarized in Table 1. Patients with SAHE were older, had a higher rate of aspirin use and lower aspirin resistance units, a higher rate of warfarin use, more lobar location of hemorrhage, larger hemorrhages with more frequent intraventricular and subdural extension, and lower Glasgow Coma Scale scores. These variables were used for adjustment in the secondary analysis. Fever and seizures were more frequent. The rate of death by day 14 was higher, and mRS scores at 28 days and at 3 months were higher for patients with SAHE.

The primary analysis looked for an association between SAHE and outcome at 3 points—death by day 14, functional outcomes measured by mRS at 28 days, and mRS at 3 months—after correction for the ICH score. SAHE was associated with increased odds of death by day 14 (adjusted odds ratio [OR], 4.45; 95% confidence interval [CI], 1.88–10.53; P=0.001) and higher (worse) mRS score at 28 days (adjusted OR, 1.76; 95% CI, 1.01–3.05; P=0.045) in the 211 (90%) patients with available 28-day mRS data. At 3 months, there was a similar but attenuated association (OR, 1.46; 95% CI, 0.82–2.59; P=0.20) in the 190 (81%) patients with 3-month mRS data. The secondary analysis using empirically identified variables from the univariate analysis confirmed the independent association between SAHE and death (adjusted OR, 7.58; 95% CI, 1.57–36.7; P=0.012). The results of the univariate analysis are shown in Table 1, and the multivariate analyses results are shown in Table 2.

Discussion

Our data demonstrate that SAHE is associated with antiplatelet and anticoagulant medication use, lower platelet activity, and independently associated with death by day 14 and worse functional outcomes at 28 days for patients with primary intracerebral hemorrhage. Although patients with SAHE have higher hematoma volumes, higher incidence of intraventricular and subdural hemorrhage extension, and lower Glasgow Coma Scale, SAHE remained significant after adjustment for those and other predictive variables.

SAHE may lead to worse functional outcome by way of increasing the odds of fever, and possibly by causing electrocortical dysfunction. In our cohort, the rate of fever was significantly higher in subjects with SAHE. Fever has been implicated in early neurological deterioration in ICH, and it is associated with worse outcomes after both ICH and aneurysmal subarachnoid hemorrhage (aSAH).13–16 Further study is needed to evaluate the role of SAHE in the development of fevers. A nonsignificant trend for higher seizure incidence in patients with SAHE also was observed. Given the association between seizures, periodic discharges, and worse outcomes in ICH and aSAH, further research may be informative.17–20 FEVERs and seizures also may serve as markers of injury to the cerebral cortex and hypothalamus, rather than a direct cause of injury.

The effect of subarachnoid blood deposition has been most carefully studied in aSAH. Whereas vasospasm leading to delayed cerebral ischemia has been considered the primary source of morbidity, many pathways are known by which extension of blood into the subarachnoid space could trigger further neurological injury in patients without overt vasospasm. Clinical experience with clazosentan in aSAH, in which vasospasm is reduced in treated patients, has helped identify and clarify the clinical impact of vasospasm-independent injury.21–23
**Table 1. Comparison of Patients With and Without Subarachnoid Hemorrhage Extension**

<table>
<thead>
<tr>
<th></th>
<th>SAHE</th>
<th>No SAHE</th>
<th>Univariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients, n</strong></td>
<td>93</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td><strong>Age, mean, SD</strong></td>
<td>68.8±14.4</td>
<td>62.6±14.0</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Sex (male), n (%)</strong></td>
<td>38 (40.9%)</td>
<td>77 (54.6%)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Race/ethnicity, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>36 (38.7%)</td>
<td>73 (51.8%)</td>
<td>0.20</td>
</tr>
<tr>
<td>White</td>
<td>42 (45.2%)</td>
<td>56 (39.7%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (9.7%)</td>
<td>8 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>6 (6.5%)</td>
<td>4 (2.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Medical history, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid mRS, median (IQR)</td>
<td>0 (0–1)</td>
<td>0 (0–0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>6 (6.5%)</td>
<td>3 (2.1%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>12 (12.9%)</td>
<td>19 (13.5%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>21 (22.6%)</td>
<td>22 (15.6%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (11.8%)</td>
<td>8 (5.7%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65 (69.9%)</td>
<td>110 (78.0%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (17.2%)</td>
<td>28 (19.9%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4 (4.3%)</td>
<td>3 (2.1%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Pack-years smoked, median (IQR)</td>
<td>0 (0–10)</td>
<td>0 (0–5)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Antithrombotic medication use and associated laboratory results**

<table>
<thead>
<tr>
<th></th>
<th>SAHE</th>
<th>No SAHE</th>
<th>Univariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole-aspirin, n (%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>43 (46.2%)</td>
<td>37 (26.2%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Aspirin resistance units, median (IQR)</td>
<td>514 (438–630)</td>
<td>591 (484–643)</td>
<td>0.004</td>
</tr>
<tr>
<td>Clopidogrel, n (%)</td>
<td>8 (8.6%)</td>
<td>13 (9.2%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Warfarin, n (%)</td>
<td>18 (19.4%)</td>
<td>10 (7.1%)</td>
<td>0.007</td>
</tr>
<tr>
<td>International normalized ratio, median (IQR)</td>
<td>1.10 (1.00–1.20)</td>
<td>1.10 (1.00–1.20)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Initial clinical data**

<table>
<thead>
<tr>
<th></th>
<th>SAHE</th>
<th>No SAHE</th>
<th>Univariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS, median (IQR)</td>
<td>9 (6–14)</td>
<td>14 (11–15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematoma volume mL, median (IQR)</td>
<td>23.8 (10.9–46.4)</td>
<td>6.7 (3.0–16.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraventricular hemorrhage, n (%)</td>
<td>64 (68.8%)</td>
<td>69 (48.9%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Subdural hemorrhage, n (%)</td>
<td>23 (24.7%)</td>
<td>5 (3.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg (mean±SD)</td>
<td>176±40</td>
<td>187±41</td>
<td>0.04</td>
</tr>
<tr>
<td>Glucose, mg/dL (mean±SD)</td>
<td>162±69</td>
<td>143±71</td>
<td>0.054</td>
</tr>
<tr>
<td>ICH score, median (IQR)</td>
<td>2 (1–3)</td>
<td>1 (0–2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar (n,%)</td>
<td>60 (64.5%)</td>
<td>27 (19.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deep, n (%)</td>
<td>23 (24.7%)</td>
<td>91 (64.5%)</td>
<td></td>
</tr>
<tr>
<td>Infratentorial/other, n (%)</td>
<td>10 (10.8%)</td>
<td>23 (16.3%)</td>
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</tbody>
</table>

**Complications**

<table>
<thead>
<tr>
<th></th>
<th>SAHE</th>
<th>No SAHE</th>
<th>Univariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever in first 14 d, n (%)</td>
<td>65 (69.9%)</td>
<td>72 (51.1%)</td>
<td>0.005</td>
</tr>
<tr>
<td>ICH growth ≥26%, n (%)</td>
<td>14 (15.1%)</td>
<td>21 (15.9%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Seizure, n (%)</td>
<td>8 (8.6%)</td>
<td>4 (2.8%)</td>
<td>0.07</td>
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</table>

**Outcomes**

<table>
<thead>
<tr>
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<th>SAHE</th>
<th>No SAHE</th>
<th>Univariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death by day 14, n (%)</td>
<td>38 (40.9%)</td>
<td>13 (9.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS 28 d, median (IQR)</td>
<td>5 (4–6)</td>
<td>4 (3–5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mRS 3 mo, median (IQR)</td>
<td>6 (3–6)</td>
<td>4 (2–5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

GCS indicates Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; n, number; SAHE, subarachnoid hemorrhage extension; and SD, standard deviation.
Delayed cerebral ischemia in a SAH occurs frequently in the absence of, and is often incorrectly attributed to, vasospasm.24–26 Processes triggered by an inflammatory response to subarachnoid blood deposition, including microcirculatory spasm, microembolism, blood–brain barrier disruption, and cortical spreading ischemia, are clearly important.27 These processes are mediated at a cellular level by dysregulation of nitric oxide, endothelial cell injury, platelet activation and aggregation, oxidative injury, proapoptotic signals, excitotoxicity with membrane instability, interstitial edema from blood–brain barrier disruption, inflammatory cytokine production, and direct microvascular injury.43 Studies in mice with blood injected into the subarachnoid space and treated with clazosentan found that despite preserved cerebral blood flow and alleviated vasospasm, oxidative dysfunction, microthromboembolism, nitric oxide dysfunction, and neuronal injury persisted.28 Similar processes may exist after ICH, and this is an opportunity for future research.

An association has been observed between the presence of subarachnoid blood, ischemic brain injury, and poor outcomes in patients with conditions other than aSAH, including penetrating brain injury and nonpenetrating traumatic brain injury, even cases with small amounts of subarachnoid blood.29,30 Those clinical studies, taken together with research on the pathophysiology of injury in aSAH, make the association we have observed between SAHE and poor outcomes highly plausible. Our hypothesis explaining the deleterious effect of SAHE, simply stated, is that blood is a proinflammatory substance effectively contained by brain parenchyma after ICH, but extension of blood into the ventricular system or subarachnoid space exposes far more brain tissue to its deleterious inflammatory effects, thus worsening the patient’s clinical status and functional outcome.

There are several strengths worth noting about our data and study methods. All data were gathered prospectively, and the neuroimaging studies were further subjected to confirmation by both a neuroradiologist and neuroradiologist to optimize the reliability of the imaging interpretations. This cohort is relatively large, and all subjects underwent scheduled follow-up at prespecified time points to gather functional outcomes by mRS in addition to mortality information.20 SAHE was clearly defined and had excellent interrater reliability. Despite the methodological rigor, however, generalization of these results is limited by their being derived from a single center. Furthermore, SAHE was determined by CT scan, so cases with very-low-volume SAHE may have been missed. Although this probably provided a dose–threshold effect for SAHE in this study, the volume of subarachnoid blood was not quantified and no assessment was possible for a proportional risk relationship. These results should be validated by other prospective and multicenter studies.

In conclusion, we found that SAHE was associated with death by day 14 and worse functional outcomes at 28 days, independent of either traditionally recognized or empirically derived predictors of poor outcome. Higher rates of fevers and seizures were seen in patients with SAHE, and cortical dysfunction with resulting injury caused by the same processes known to affect patients with aneurysmal subarachnoid hemorrhage are suspected to mediate this in a causal relationship. Future research might determine whether these are the same processes at work, and whether complications of SAHE might be attenuated by medical interventions.

Disclosures
Dr Naidech serves as a medical safety monitor for two unrelated National Institutes of Health–funded trials and has received unrelated research funding from the Northwestern Memorial Foundation. The other authors report no conflicts.

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Stroke


Neurology


Stroke

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Stroke
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