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Predictors of hemorrhage volume and disability after perimesencephalic subarachnoid hemorrhage

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ABSTRACT

Objective: The determinants of subarachnoid hemorrhage (SAH) volume and an atypical pattern of blood are not clear. Our objective was to determine if reduced platelet activity on admission and abnormal venous drainage are associated with greater SAH volume.

Methods: We prospectively identified noncomatose patients with SAH without an identifiable aneurysm. We routinely measured platelet activity on admission and recorded aspirin use. SAH volumes were calculated with a validated technique. CT angiograms were reviewed by a certified neuroradiologist for venous drainage. Patients were followed for clinical outcomes through 3 months with the modified Rankin Scale (mRS). Data are Q1–Q3.

Results: There were 31 patients in the cohort. Thirty (97%) underwent an angiogram on admission, and 25 (81%) an additional delayed angiogram. SAH volume was lowest with normal venous drainage bilaterally (4.4 [3.7–16.4] mL) and higher with 1 (12.9 [3.7–20.4]) or 2 (20.9 [12.5–34.6]) mL, $p = 0.03$ discontinuous venous drainages. Patients with reduced platelet activity had more SAH on the diagnostic CT (17.5 [10.6–20.9] vs 6.1 [2.3–15.3] mL) ($p = 0.046$). SAH volume was greater for patients requiring drainage for hydrocephalus (16.4 [11.5–20.5] vs 5.4 [2.7–16.4] mL) ($p = 0.009$). Outcomes at 3 months were generally excellent (median mRS = 0, no symptoms).

Conclusions: Discontinuous venous drainage and reduced platelet activity were associated with increased SAH volume and hydrocephalus. These factors may explain thick SAH and reduce the need for repeated invasive imaging in such patients. Neurology® 2012;78:811–815

GLOSSARY

ARU = aspirin reaction unit; CTA = CT angiography; EVD = external ventricular drain; mRS = modified Rankin Scale; PM-SAH = perimesencephalic subarachnoid hemorrhage; SAH = subarachnoid hemorrhage.

Nontraumatic subarachnoid hemorrhage (SAH) is typically caused by rupture of an intracranial aneurysm. Perimesencephalic SAH (PM-SAH) refers to patients with scant subarachnoid blood around the brainstem and no identifiable aneurysm.1,2 Compared to patients with an identifiable aneurysm, the prognosis is generally excellent.3 Quality of life4 and life expectancy are normal.5

Not all patients without an identifiable aneurysm have a typical CT appearance, however, and repeated evaluations with CT angiography6 or catheter angiography7 are often performed to detect an occult aneurysm. It is not known why some patients have more blood on CT than others. The inter-rater reliability for a nonaneurysmal pattern of hemorrhage is only good,8 so defining atypical patients is challenging. More hemorrhage on CT than is typical for PM-SAH has been associated with an increased risk of hydrocephalus and worse outcome in some,9 but not all,10 datasets.

Altered venous drainage is associated with PM-SAH.11,12 It is not known, however, if altered venous drainage on either or both sides of the brainstem is associated with more bleeding. Another potential explanation for greater SAH volumes is aspirin use and reduced platelet...
activity because they are associated with more bleeding and worse outcome after intraparenchymal hemorrhage.\textsuperscript{13,14}

Identification of determinants of SAH volume would be helpful to identify which patients likely have PM-SAH (and its attendant excellent prognosis) or an occult aneurysm. We tested the hypotheses that reduced platelet activity and altered venous drainage are associated with a greater volume of bleeding in patients with nonaneurysmal SAH.

METHODS We prospectively identified patients from November 2006 through May 2011. SAH was diagnosed by typical clinical symptoms and acute hemorrhage detected on routine CT scanning. Patients with permanent coma, lack of intracranial blood flow due to intracranial catastrophe from aneurysm rupture, or an identified aneurysm were excluded. SAH due to trauma, arteriovenous malformation rupture, vasculitis, metastasis, and other structural lesions were excluded. All patients were admitted to a dedicated neurologic intensive care unit and evaluated by a certified neurologist and neurosurgeon.

All patients were evaluated with high-quality CT angiography (CTA) or catheter angiography in-house to detect an occult aneurysm (all but one patient underwent both on admission), interpreted by a certified neuroradiologist.

Multidetector CTA acquisition was performed according to standard protocol on either 16- or 64-section helical CT scanners. The scans were performed from the C1 vertebral body base to the vertex with the following parameters: pitch 0.5, collimation 1 mm, slice thickness 1 mm, 340 mAs, 120 kVp, field of view 20 cm, matrix 512 × 512, and 65-ml nonionic contrast agent administered by power injector at 4 ml per second into an antecubital vein after a test bolus was given to determine the scan delay. The analysis of venous drainage was performed in 30 of 31 (97%) patients with the study performed. In 13 of the 30 cases 3-mm-thick maximum intensity projection axial reconstructions were available. Drainage was classified as previously described by others\textsuperscript{11,13} as normal, discontinuous on the left or right, or primitive by a single certified neuroradiologist (A.J.N.) who was blinded to clinical variables and outcomes.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Board and all patients or a legally authorized representative gave written consent.

Clinical variables were prospectively collected. We recorded baseline demographic and past medical history data onto standardized forms. The intensive care unit pharmacist routinely performed medication reconciliation with the patient and surrogates, and aspirin use was prospectively recorded. (No patient was known to take clopidogrel.) We recorded a history of hypertension as documented outpatient blood pressure >135/90 mm Hg or prescribed antihypertensive medication, and a history of diabetes as documented outpatient diagnosis or prescribed hypoglycemic medication. A history of coronary artery disease was defined as a history of revascularization or documented myocardial ischemia. We prospectively recorded if an external ventricular drain (EVD) was required for clinical hydrocephalus, and the occurrence of clinical vasospasm (new focal neurologic deficit or depressed mental status without other explanation).

RESULTS Demographics of the cohort are shown in the table. Thirty (97%) patients underwent an angiogram on admission, and 25 (81%) at least 1 additional delayed angiogram, and 3 (10%) a third angiogram prior to discharge. No patient had a history of atrial fibrillation, warfarin use, or clopidogrel use. Any known aspirin use was associated with increased odds of reduced platelet activity; odds ratio 14 (95% confidence interval 1.3–150.9, \( p = 0.049 \)).

For the entire cohort, the measured SAH volume was 11.5 (3.8–19.5) mL. Less platelet activity was correlated with a greater SAH volume (Spearman rho −0.526, \( p = 0.007 \)). Patients with reduced platelet activity had more SAH volume than patients with normal platelet activity, 17.5 (10.6–20.9) vs 6.1 (2.3–15.3) mL (\( p = 0.046 \), figure 1). The results were similar for patients known to take any aspirin vs not, 18.5 (5.1–21.9) vs 11.2 (3.8–16.4) mL (\( p = 0.2 \)). The 25 (81%) patients prospectively noted as having thick (modified Fisher grade III)\textsuperscript{18} (as op
posed to thin, grade I) subarachnoid blood had a
greater volume of SAH, 14.8 (4.2–20.4) vs 5.4 (0.5–
8.8) mL (p/H11005 0.04). No patient had intraventricular
hemorrhage.

SAH volume was lowest with normal venous
drainage (4.4 [3.7–16.4] mL) and higher with 1
(12.9 [3.7–20.4]) or 2 (20.9 [12.5–34.6] mL, p
/H11005 0.03) discontinuous venous drainages (figure 1). Ve-
nous drainage and reduced platelet activity were not
correlated (p = 0.6). The availability of maximum
intensity projection images was not associated with
the classification of venous drainage or SAH volume.

Eleven (35%) patients required placement of an
EVD for clinical hydrocephalus. These patients had
more SAH than those who did not undergo EVD
placement, 16.4 (11.5–20.5) vs 5.4 (2.7–16.4) mL
(p = 0.009). One patient developed symptomatic
vasospasm.

Greater SAH volume (p = 0.02) and reduced
platelet activity (p = 0.04) were related to an in-
creased mRS at 14 days (figure 2). At 3 months only
2 patients had mild disability (mRS 2) and only 1
was nonindependent (mRS 4), while the rest had no
symptoms. No patient was eventually found to have an
intracranial aneurysm.

**DISCUSSION** We found that reduced platelet ac-
activity (consistent with aspirin use) and discontinuous
venous drainage were associated with more SAH in
noncomatose patients without an identifiable aneu-
rysm. These results are intuitive because aspirin is
associated with more bleeding and worse acute out-
comes in patients with intraparenchymal hemor-
rhage,13,14 while discontinuous venous drainage
might lead to more severe bleeding if there is a ve-
nous rupture. These data may explain why a substan-
tial proportion of patients with SAH and no
identifiable aneurysm have more SAH than would be
expected (“diffuse” or “thick” PM-SAH as opposed
to typical PM-SAH) and may have a course compi-
lcated by hydrocephalus or vasospasm.9 These data sug-
gest that not all patients with thick SAH require
multiple invasive imaging studies if there is another ex-
planation (measured reduced platelet activity, known
aspirin use, or discontinuous venous drainage).

Greater SAH volume was associated with more
disability at 14 days and placement of an EVD for
hydrocephalus, and such a result might be reasonably
expected. While more SAH volume was associated
with the perceived clinical need for an EVD, this is
not strictly the same as hydrocephalus. Even with the
more complicated acute course, no patients died and
clinical outcomes were excellent, consistent with the
known history of PM-SAH.2 Despite the increased
SAH volume with reduced platelet activity, the lack
of bleeding from an arterial source makes an excellent
outcome likely.

While aspirin was associated with reduced platelet
activity, it was not significantly associated with
greater SAH volume. Aspirin is unlikely to be the
only antiplatelet medication taken, and we the pa-
tient may not have reported a single dose for head-
ache. Over-the-counter pain medications (e.g.,
ibuprofen) will also lead to reduced platelet activity21
and might reasonably be taken for the headache that
accompanies PM-SAH. Aspirin and ibuprofen are
not detected on routine toxicology screens, and a disori-
dented patient might not be able to provide an over-the-
counter medication history, so point-of-care testing is
likely to be more sensitive. (We have made a similar
observation in patients with intraparenchymal hemor-
rhage.22) Measured salicylate levels might have been
helpful to detect surreptitious aspirin use.

We prospectively graded the pattern of subarach-
noid blood,16 but did not attempt to define the pat-

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**Table Demographics of the 31 patients in the study**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.9 ± 13.9</td>
</tr>
<tr>
<td>WFNS grade 1</td>
<td>26 (84)</td>
</tr>
<tr>
<td>WFNS grade 2</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Women</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Symptom onset to CT, d</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>19 (61)</td>
</tr>
<tr>
<td>African American</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>15 (48)</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>4 (13)</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>23 (74)</td>
</tr>
<tr>
<td>81 mg</td>
<td>1 (3)</td>
</tr>
<tr>
<td>325 mg or more</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Venous drainage</td>
<td></td>
</tr>
<tr>
<td>Normal bilaterally</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Discontinuous on one side</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Discontinuous on both sides</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Any primitive drainage</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Evaluated with angiography on admission</td>
<td>30 (97)</td>
</tr>
<tr>
<td>Additional delayed angiography in house</td>
<td>25 (81)</td>
</tr>
</tbody>
</table>

Abbreviation: WFNS = World Federation of Neurological Surgeons.

a In the 30 patients who underwent CT angiography.
tern of subarachnoid blood as perimesencephalic or diffuse because the inter-rater reliably of such a comparison is not excellent. Measuring the volume of subarachnoid blood with a validated technique may be more informative than its pattern, and we demonstrated a high inter-rater correlation. While some clinicians might not consider patients with thick SAH or a diffuse pattern of SAH to have PM-SAH, we found that such patients usually have its benign clinical course and outcome.

We excluded permanently comatose patients because PM-SAH typically occurs in good-grade patients. The inability to find an aneurysm in a comatose patient with SAH may indicate there is no cerebral blood flow, a requirement for angiography or CTA, and this may be a different patient population from the one described here. In our registry, the outcome for 6 such patients was death by neurologic criteria. Two such other excluded patients were dependent at 14 days, mRS 4 and 5, and survived to discharge but their surrogates declined consent to record identifiers and obtain follow-up. This patient population may require further study.

Strengths of this work include prospective identification of patients with outcomes after discharge, routine measurement of platelet activity, routine performance of CTA with interpretation of venous drainage by a blinded certified interpreter with a previously published classification, medication reconciliation on admission, and volumetric analysis of CT scans with a validated technique. Potential weaknesses of these data include the ascertainment of patients at only one center and the modest number of patients. The diagnosis of nonaneurysmal SAH, however, should not substantially vary between institutions. Not all methods of platelet activity testing are equivalent; the method we used performs closest to platelet aggregometry,23 is Food and Drug Administration–approved to detect an aspirin effect, is relatively inexpensive, and can be easily measured during off hours. These tabletop assays should have excellent test-retest reliability when calibrated per the manufacturer instructions. We did not routinely measure salicylate levels, although this might be helpful to exclude aspirin use. The interpretation of venous drainage from CTA should also be similar at different institutions. We only analyzed the diagnostic CT, not subsequent CT scans, and so have no data on the evolution of SAH volumes over time. We relied on published methods for the analysis of venous drainage from CT, but did not perform dedicated catheter venograms, which might be more accurate for the detection of aberrant venous drainage.

We found that reduced platelet activity and discontinuous venous drainage were associated with...
more SAH in patients without an identifiable aneurysm. When thick SAH is seen on CT in a patient without an identifiable aneurysm, reduced platelet activity or discontinuous venous drainage are potential explanations and may obviate the need for serial invasive imaging studies; even if clinical hydrocephalus leads to EVD placement, such patients are likely to have an excellent outcome.

**AUTHOR CONTRIBUTIONS**

A.M.N. performed some volumetric measurements, performed the analysis, and wrote the first draft of the manuscript. N.F.R. performed some volumetric measurements and revised the manuscript. M.B.M. revised the manuscript. H.H.B. revised the manuscript. A.J.N. interpreted CT angiograms and revised the manuscript. A.M.N. performed the statistical analysis.

**DISCLOSURE**

Dr. Naidech serves as a medical safety monitor for the NIH and has received research support from the Northwestern Memorial Foundation, Gaymar Inc., and Astellas Pharma Inc. Dr. Rosenberg and Dr. Maas report no disclosures. Dr. Bendok receives research support from Microvention. Dr. Batjer and Dr. Nemeth report no disclosures.

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