Cerebral Vasospasm Due to Arteriovenous Malformation-Associated Hemorrhage: Impact of Bleeding Source and Pattern

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Abstract
Objective: Cerebral vasospasm (CVS) after a ruptured arteriovenous malformation (AVM) is rarely reported. This study is aimed at evaluating the predictive variables in AVM hemorrhage for CVS. Methods: A total of 160 patients with ruptured AVMs were admitted to our neurosurgical department from 2002 to 2018. The frequency of cerebral vasospasm after AVM hemorrhage and the impact of AVM-associated aneurysms were evaluated. We compared different bleeding patterns, such as intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH) or a combination of both (ICH + SAH) and evaluated predictive variables for outcome in last follow-up. Results: A total of 62 (39%) patients had AAA, mostly located prenidal (75.8%). AVMs with ruptured aneurysms often resulted in ICH with SAH component (p < 0.001). Eighty-two patients (51%) presented a SAH component, and CVS occurred in 6 patients (7.3%), mostly due to a ruptured infratentorial AVM (p < 0.03). Infratentorial location and the amount of SAH component (p < 0.001) predicted the incidence of CVS significantly. Cerebral infarction was significantly associated with CVS (p < 0.02). Conclusion: SAH component and infratentorial location of ruptured AVMs may harbor a higher risk for CVS. Follow-up with angiographic imaging should be considered in patients with infratentorial AVM hemorrhage and delayed neurologic deterioration to rule out CVS.

Introduction

Cerebral vasospasm (CVS) is uncommon in arteriovenous malformation (AVM)-associated hemorrhage and could be an undetected reason for patients’ worsening during the course. Depending on AVM angioarchitecture and location, the risk for CVS may rise. The amount of subarachnoid blood is a commonly accepted reason for CVS in aneurysmal subarachnoid hemorrhage (SAH) [1]. Nevertheless, reports of CVS after SAH due to a ruptured AVM are rare and pathophysiology is not well described. In the current literature, the rate of vasospasm after SAH from AVMs is between 1.9 and 12% [2]. The aim of our
study was to assess the incidence of CVS after AVM-associated hemorrhage for detecting the predictive variables and to describe prognostic factors in treatment decisions.

Materials and Methods

Study Population

The study was performed in accordance with our institutional ethical review board. We performed a retrospective analysis of patients with ruptured brain AVM who were registered and evaluated at our neurosurgical department from 2002 to 2018 and entered into our prospective maintained database. Inclusion criteria included ruptured brain AVM, confirmed by magnetic resonance imaging (MRI) or digital subtraction angiography (DSA), complete demographic data, and follow-up information. Patient’s gender, age, admission grade based on the Glasgow Coma Scale, bleeding pattern, clinical course and outcome were recorded and evaluated.

Radiological and AVM Features

All patients received at least a computed tomography (CT) to confirm bleeding. Further diagnostics included MRI and DSA. Imaging was performed and interpreted by an experienced neuroradiologist. Data were abstracted from the medical and radiological reports. The bleeding pattern was categorized as follows: isolated intracerebral hemorrhage (ICH) or SAH or a combination of both (ICH + SAH). In cases of SAH, the primary modified Fisher score (mFisher) was recorded. The occurrence of CVS was recorded with CT angiography, MRI or DSA. In one case, the results of the transcranial doppler ultrasound were suspicious for CVS and further imaging was initiated. We classified CVS according to the degree of arterial narrowing (%) into mild (<50 cm/s), moderate (50–150 cm/s), and severe (>150 cm/s) or >50 cm/s in 24 h was suspicious for CVS and unfavorable outcome were entered into a forward stepwise multiple logistic regression analysis. Statistical significance was set at \( p < 0.05 \).

Results

Demographic Characteristics and AVM Features

Demographic data, radiologic findings, and AVM features are listed in Table 1.

A total of 160 patients with ruptured brain AVMs were included and reviewed. The patient’s mean age was 42 years. A total of 106 (66%) patients were admitted in a good clinical condition (Glasgow Coma Scale >12).

A Spetzler Martin grade 1–3 was present in 143 (89%) patients, and angiography showed AAA in 62 (39%) AVMs. In 47 (76%) cases, an arterial prenidal aneurysm could be detected. Venous intra-/postnidal aneurysms were present in 15 (24%) AVMs. Venous aneurysms were mostly located supratentorial (87 vs. 13%; \( p = 0.01 \)).

The majority of AVMs had a deep venous drainage system (94; 59%) and was located supratentorial (111; 69%). The rate of ruptured AAA was infratentorial higher than supratentorial (88.5 vs. 58.3%; \( p = 0.01 \)).

In general, prenidal aneurysms tended to rupture more often compared to postnidal aneurysms (91.1 vs. 8.9%; \( p < 0.0001 \)).

Definition of CVS and Cerebral Infarction

CVS was defined as an arterial narrowing shown on angiographic imaging (CT angiography, MRI, DSA) compared to the baseline angiograms. In transcranial doppler findings, an increased flow velocity of >150 cm/s or >50 cm/s in 24 h was suspicious for CVS and further imaging was initiated. We classified CVS according to the degree of arterial narrowing (%) into mild (<30%), moderate (30–60%), and severe (>60%). In cases of confirmed CVS, hypertension was induced with norepinephrine infusions. A cerebral infarction (CI) was defined as a new hypodensity on CT or MRI during the hospital stay, which was not related to surgery or angiogram.

Follow-Up and Outcome

We recorded the occurrence of CVS and CI during the course and evaluated the relation to patients and hemorrhage characteristics. Outcome, based on the modified Rankin Scale (mRS), was classified as favorable (mRS 0–2) and unfavorable (mRS 3–6).

Statistical Analysis

Statistical analysis was performed using the statistical software packages SPSS (IBM SPSS Statistics for Windows, Version 22; Armonk, NY, USA. IBM Corp.) and BIAS (Version 11.08). Categorical variables were analyzed in contingency tables using the Fisher exact test, an unpaired t test was used for parametric statistics. For univariate analysis, statistical significance was set at \( p < 0.05 \). Variables with a possible association with CVS and unfavorable outcome were entered into a forward stepwise multiple logistic regression analysis. Statistical significance was set at \( p < 0.05 \).
were statistically significant in the prediction of CVS ($p < 0.0001$). The referring data are summarized in Table 3a. CI occurred in 10 (6.3%) patients and was significantly associated with the incidence of CVS (OR 11.16 [1.8–69.3]; $p = 0.02$). Figure 1a–h demonstrates the case of a patient who suffered CVS and CI during the further course after AVM-associated hemorrhage.

**Outcome**

A total of 121 (76%) patients achieved a favorable outcome. Neurological condition at admission ($p < 0.001$), the mFisher score ($p < 0.001$), hematoma volume ($p = 0.005$), and infratentorial location ($p = 0.02$) had the strongest significant influence on the final outcome.

**Discussion**

The aim of our study was to find the predictive variables for CVS in AVM-associated hemorrhage. In aneurysmal SAH, CVS and CI are common [3–7], owing to the amount of subarachnoid blood [1, 7–11]. AVMs show differences in hemorrhage pattern and clinical course in relation to bleeding pattern (SAH, ICH), their location, and angioarchitecture [12]. Although SAH is one of the bleeding pattern in AVM-associated hemorrhage [13, 14], CVS thereafter is rarely described in the pertaining literature and limited to a few case reports mostly associated with intraventricular hemorrhage [15–18]. Gross et al. [2] described in their study one case (3.7%) of mild vasospasm after AVM rupture. In their review of the literature, the rate of vasospasm after AVM rupture ranged between 1.9 and 12% and revealed an overall 6.3% rate of vasospasm. All cases had intraventricular hemorrhage, no patient experienced CI. In our study SAH component occurred in 51% of the patients, and 6 patients experienced CVS (7.3%). CVS was confirmed by angiography, only in 1 patient CVS was detected with CT-angiography. CVS was usually of mild or moderate degree. In 5 of 6 patients, CVS occurred in infratentorial AVM-associated hemorrhage due to a ruptured arterial prenidal aneurysm (Table 2). Venous postnidal aneurysm rupture did not lead to CVS and IVH did not predict CVS significantly. The pressure of blood when entering the subarachnoid space during the rupture of arterial vessels is thought to be a reason for CVS after aneurysmal SAH [2]. This theory could explain the development of CVS after rupture of a prenidal arterial aneurysm in AVMs.

In the literature, AAA are described as risk factors for hemorrhage [19–21]. The prevalence of AAAs amounts 10–30% [19, 22, 23]. In our study, the rate of AAAs in ruptured AVMs was 38.8%. The hemorrhage risk with AAAs is described to be 63.6% compared to 50% without an associated aneurysm [24, 25].

Furthermore, 10 patients experienced CI during hospital stay and CI was significantly associated with the incidence of CVS. In 2 of 10 patients, we could not perform angiography to detect or rule out CVS. Thus, the reason for CI remained unclear in these patients.

The reason why vasospasm seldom occurs after AVM rupture remains poorly explained. Differences in hemodynamics and pressure differences in aneurysms and arterio-
venous vessels are described [2]. Furthermore, infratentorial arterial aneurysmal hemorrhage may lead to CVS in AVMs, and flow monitoring via at least transcranial sonography should be performed. Especially in cases with delayed neurological deficits and CI during the course, the occurrence of CVS should be considered and ruled out.

**Limitations**

The retrospective study design is one limitation of our study. Since the study design was retrospective, we did not perform angiography routinely in AVM patients with subarachnoid blood after day 4 just to rule out vasospasm. Our statements regarding the occurrence of vasospasm are based on the collected data.

**Table 2.** Data of patients with cerebral vasospasm

<table>
<thead>
<tr>
<th>Patients</th>
<th>n</th>
<th>Hemorrhage pattern</th>
<th>Ruptured AAA</th>
<th>Vessels in spasm</th>
<th>Spasm degree</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Female, years</td>
<td>16</td>
<td>SAH, IVH, mFisher 4</td>
<td>None</td>
<td>BA</td>
<td>Mild</td>
<td>None</td>
</tr>
<tr>
<td>2 Male</td>
<td>50</td>
<td>SAH, mFisher 3</td>
<td>PICA</td>
<td>PICA</td>
<td>Mild</td>
<td>None</td>
</tr>
<tr>
<td>3 Male</td>
<td>53</td>
<td>SAH, IVH, mFisher 4</td>
<td>PICA</td>
<td>VA, BA, PCA</td>
<td>Moderate</td>
<td>Brainstem</td>
</tr>
<tr>
<td>4 Female</td>
<td>46</td>
<td>ICH, SAH, mFisher 3</td>
<td>BA</td>
<td>BA, PICA</td>
<td>Severe</td>
<td>MCA, PCA</td>
</tr>
<tr>
<td>5 Male</td>
<td>72</td>
<td>SAH, IVH, mFisher 4</td>
<td>PICA</td>
<td>BA</td>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>6 Male</td>
<td>46</td>
<td>SAH, IVH, mFisher 4</td>
<td>BA</td>
<td>BA, PCA, MCA</td>
<td>Severe</td>
<td>ACA, MCA</td>
</tr>
</tbody>
</table>

mFisher, modified Fisher score; AAA, arteriovenous malformation-associated aneurysm; BA, basilar artery; PICA, posterior inferior cerebellar artery; VA, vertebral artery; PCA, posterior cerebral artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.

**Table 3.**

a CVS-associated variables in univariate and multivariate analyses

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>GCS &lt;13</td>
<td>10.7 (1.2–94.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>mFisher 3 + 4</td>
<td>3.5 (2.7–4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>12.5 (1.4–110.0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* NA, not applicable.

GCS, Glasgow Coma Scale; mFisher, modified Fisher score; ns, not significant.

b Predictive variables for final (favorable) outcome

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>GCS &gt;12</td>
<td>26.2 (9.7–70.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVS*</td>
<td>0.06 (0.00–0.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>mFisher 0–2**</td>
<td>4.3 (2.0–9.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematoma volume &lt;30 cm³</td>
<td>9.5 (4.1–21.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supratentorial location</td>
<td>3.3 (1.6–7.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>IVH*</td>
<td>0.4 (0.2–0.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>CI**</td>
<td>0.1 (0.02–0.5)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* The occurrence of CVS/IVH/CI is associated with unfavorable outcome in univariate analysis.

** mFisher, modified Fisher score.

GCS, Glasgow Coma Scale; CVS, cerebral vasospasm; AAA, arteriovenous malformation-associated aneurysm; IVH, intraventricular hemorrhage; CI, cerebral infarction; ns, not significant.
sospasm are based on patients' clinical condition and routine and established radiological methods using MRI and DSA after AVM treatment or for the purpose of follow-up. Patients with confirmed CVS received DSA, except 1 patient. Nevertheless, the high number of our study patients with appropriate and uniformly performed diagnostic methods and follow-up data in one center strengthens the evidence of our results. Furthermore the considerable number of CVS in our study population is higher than in the current literature and should support further studies.

**Conclusion**

CVS seems to be a complication in SAH after AVM hemorrhage, in particular, in infratentorial AVMs. We recommend flow monitoring and angiographic imaging in AVM hemorrhage with SAH component, especially in cases of delayed neurological deterioration during the hospital stay.

**Ethical Approval**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee (University Hospital Frankfurt) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Disclosure Statement**

The authors declare that there is no conflict of interest.

**Informed Consent**

For this type of study, formal consent is not required.
References


