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.

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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

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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 substraction 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 additional angiogram confirmed CVS. The location of the hemorrhage and the AVM were categorized as supratentorial or infratentorial. For computer-assisted volumetric measurements of ICH, the BrainLab® elements software (BrainLab Germany Headquarters, Munich, Germany) was used. AVMs were classified according to the Spetzler Martin grading system. AVM features such as size, the existence of arteriovenous malformation-associated aneurysms (AAA), and deep venous drainage were recorded. AAAs were divided into prenidal arterial and intra-/postnidal venous aneurysms.

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 $p < 0.05$.

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%; $p < 0.0001$).

CVS and CI

The mean hematoma volume was 34.80 cm³, and isolated SAH was present in 20% of cases. In total, 82 (51%) patients had a SAH component. Intraventricular hemorrhage (IVH) occurred in 78 (49%) cases and was not associated with CVS in statistical analysis. Six patients experienced CVS during the clinical course (6/82 = 7.3%). The mean time between ictus and the occurrence of CVS was 6 days (range between 3 and 9 days). Five of six patients with CVS had an infratentorial AVM and hemorrhage was due to a prenidal aneurysm. Data of patients with CVS are presented in Table 2. Univariate analysis demonstrated that the first admission state ($p = 0.02$), infratentorial location ($p = 0.03$), and the amount of SAH component in bleeding pattern with or without IVH (mFisher 3 + 4)

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Table 1. Demographic characteristics of 160 patients with AVM hemorrhage

Number of patients	160
Clinical features	
Gender, female	80 (50)
Age, years, mean (range)	42 (2–82)
GCS admission >12	106 (66)
mRS – favorable (0–2)	121 (76)
Mean length of observation, months	24
AVM features	
Spetzler Martin 1	27 (17)
Spetzler Martin 2	53 (33)
Spetzler Martin 3	63 (39)
Spetzler Martin 4	14 (9)
Spetzler Martin 5	3 (2)
Aneurysm	63 (39)
Not AVM associated	1
AVM associated	62
Arterial/prenidal	47 (76)
Venous/postnidal	15 (24)
Deep drainage	94 (59)
AVM location	
Supratentorial	111 (69)
Infratentorial	49 (31)
Hemorrhage characteristics	
Mean hemorrhage volume, cm^3	34.80
mFisher	
0	78 (49)
1	23 (14)
2	9 (6)
3	10 (6)
4	40 (25)
IVH	78 (49)
CI	10 (6)
CVS	6 (7.3)*

* CVS in SAH patients (6/82).

GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; CVS, cerebral vasospasm; mFisher, Modified Fisher score; IVH, intraventricular hemorrhage; CI, cerebral infarction; AVM, arteriovenous malformation.

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-

Table 2. Data of patients with cerebral vasospasm

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

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

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
GCS <13	10.7 (1.2–94.2)	0.02	ns	ns
mFisher 3 + 4	3.5 (2.7–4.5)	<0.001	NA*	<0.0001
Infratentorial location	12.5 (1.4–110.0)	0.01	0.1 (0.01–1.1)	0.03

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

b Predictive variables for final (favorable) outcome

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
GCS >12	26.2 (9.7–70.4)	<0.001	12.3 (4.2–36.2)	<0.001
CVS*	0.06 (0.00–0.5)	0.003	ns	ns
mFisher 0–2**	4.3 (2.0–9.2)	<0.001	ns	ns
Hematoma volume <30 cm^3	9.5 (4.1–21.9)	<0.001	4.5 (1.5–13.3)	0.005
Supratentorial location	3.3 (1.6–7.1)	0.002	3.4 (1.2–9.6)	0.02
IVH*	0.4 (0.2–0.8)	0.02	ns	ns
CI*	0.1 (0.02 –0.5)	0.002	ns	ns

* The occurence 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.

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 va-

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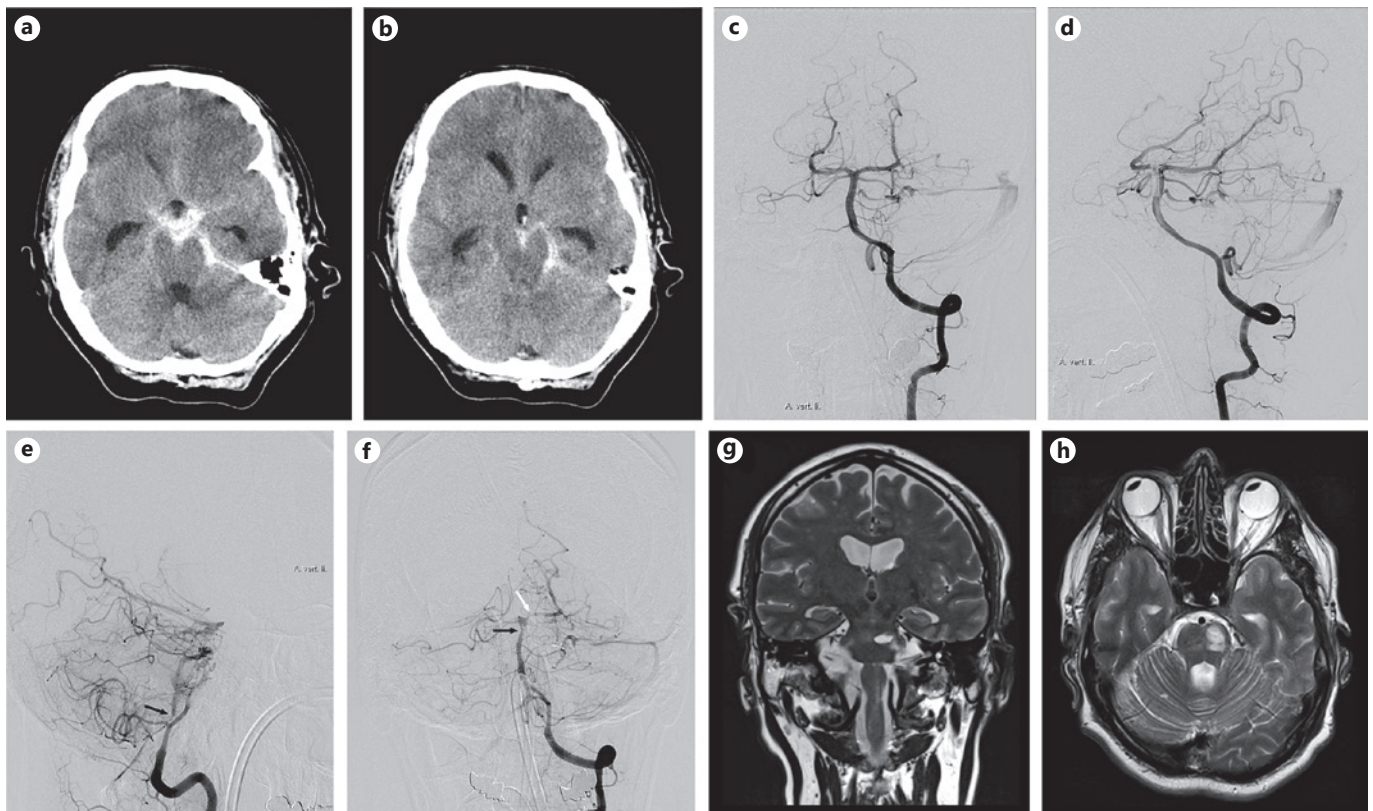
Fig. 1. a, **b** CT image shows diffuse subarachnoid hemorrhage of the basal cisterns. **c**, **d** Selective cerebral angiography revealed an AVM with feeding vessels from the basilar artery and superior cerebellar artery. A ruptured AVM-associated prenidal aneurysm was found as the origin of the bleeding. **e**, **f** The angiography in different projections demonstrates CVS of the vertebral artery, basilar artery (black arrow), and posterior cerebral artery (white arrow). CVS occurred at day 8 and was in mild degree. **g**, **h** Signal intensity in the left side of the brain stem is shown in MRI follow-up (axial T2 stack).

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

1 Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery. 1980 Jan; 6(1):1–9.

2 Gross BA, Du R. Vasospasm after arteriovenous malformation rupture. World Neurosurg. 78(3-4):300–5.

3 Jabbarli R, Reinhard M, Roelz R, Shah M, Niesen WD, Kaier K, et al. Early identification of individuals at high risk for cerebral infarction after aneurysmal subarachnoid hemorrhage: the BEHAVIOR score. J Cereb Blood Flow Metab. 2015 Oct;35(10):1587–92.

4 Schmidt JM, Rincon F, Fernandez A, Resor C, Kowalski RG, Claassen J, et al. Cerebral infarction associated with acute subarachnoid hemorrhage. Neurocrit Care. 2007;7(1):10–7.

5 Rabinstein AA, Friedman JA, Weigand SD, McClelland RL, Fulgham JR, Manno EM, et al. Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke. 2004 Aug;35(8):1862–6.

6 Crowley RW, Medel R, Dumont AS, et al. Angiographic vasospasm is strongly correlated with cerebral infarction after subarachnoid hemorrhage. Stroke. 2011 Apr;42(4):919–23.

7 Darkwah Oppong M, Iannaccone A, Gembruch O, Pierscianek D, Chihi M, Dammann P, et al. Vasospasm-related complications after subarachnoid hemorrhage: the role of patients' age and sex. Acta Neurochir (Wien). 2018 Jul;160(7):1393–400.

8 Inagawa T. Risk Factors for Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage: A Review of the Literature. World Neurosurg. 2016 Jan;85:56–76.

9 Ryttlefors M, Enblad P, Ronne-Engström E, Persson L, Ilodigwe D, Macdonald RL. Patient Age and Vasospasm After Subarachnoid Hemorrhage. Neurosurgery. 2010 Oct;67(4): 911–7.

10 Lagares A, Jiménez-Roldán L, Gomez PA, Munarriz PM, Castaño-León AM, Cepeda S, et al. Prognostic Value of the Amount of Bleeding After Aneurysmal Subarachnoid Hemorrhage: A Quantitative Volumetric Study. Neurosurgery. 2015 Dec;77(6):898–907.

11 Friedman JA, Goerss SJ, Meyer FB, Piepgras DG, Pichelmann MA, McIver JI, et al. Volumetric quantification of Fisher Grade 3 aneurysmal subarachnoid hemorrhage: a novel method to predict symptomatic vasospasm on admission computerized tomography scans. J Neurosurg. 2002 Aug;97(2):401–7.

12 Dinc N, Eibach M, Tritt S, Konczalla J, Seifert V, Marquardt G. Special Features in AVMs. Impact of Draining Veins on Hemorrhagic Presentation. Ann Vasc Med Res. 2017;4.

13 Locksley HB, Sahs AL, Knowler L. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section II. General survey of cases in the central registry and characteristics of the sample population. J Neurosurg. 1966 May;24(5):922–32.

14 Perret G, Nishioka H. Report on the cooperative study of intracranial aneurysms and subarachnoid hemorrhage. Section VI. Arteriovenous malformations. An analysis of 545 cases of cranio-cerebral arteriovenous malformations and fistulae reported to the cooperative study. J Neurosurg. 1966 Oct;25(4): 467–90.

15 Lobato RD, Gomez PA, Rivas JJ. Arteriovenous malformations and vasospasm. J Neurosurg. 1998 May;88(5):934–5.

16 Yanaka K, Hyodo A, Tsuchida Y, Yoshii Y, Nose T. Symptomatic cerebral vasospasm after intraventricular hemorrhage from ruptured arteriovenous malformation. Surg Neurol. 1992 Jul;38(1):63–7.

17 Maeda K, Kurita H, Nakamura T, Usui M, Tsutsumi K, Morimoto T, et al. Occurrence of severe vasospasm following intraventricular hemorrhage from an arteriovenous malformation. Report of two cases. J Neurosurg. 1997 Sep;87(3):436–9.

18 Pendharkar AV, Guzman R, Dodd R, Cornfield D, Edwards MS. Successful treatment of severe cerebral vasospasm following hemorrhage of an arteriovenous malformation. Case report. J Neurosurg Pediatr. 2009 Sep;4(3): 266–9.

19 Platz J, Berkefeld J, Singer OC, Wolff R, Seifert V, Konczalla J, et al. Frequency, risk of hemorrhage and treatment considerations for cerebral arteriovenous malformations with associated aneurysms. Acta Neurochir (Wien). 2014 Nov;156(11):2025–34.

20 Stein KP, Wanke I, Forsting M, Zhu Y, Moldovan AS, Dammann P, et al. Associated aneurysms in supratentorial arteriovenous malformations: impact of aneurysm size on haemorrhage. Cerebrovasc Dis. 2015;39(2): 122–9.

21 Stein KP, Wanke I, Forsting M, Oezkan N, Huetter BO, Sandalcioglu IE, et al. Associated Aneurysms in Infratentorial Arteriovenous Malformations: Role of Aneurysm Size and Comparison with Supratentorial Lesions. Cerebrovasc Dis. 2016;41(5–6):219–25.

22 Flores BC, Klinger DR, Rickert KL, Barnett SL, Welch BG, White JA, et al. Management of intracranial aneurysms associated with arteriovenous malformations. Neurosurg Focus. 2014 Sep;37(3):E11.

23 Shakur SF, Amin-Hanjani S, Mostafa H, Charbel FT, Alaraj A. Hemodynamic Characteristics of Cerebral Arteriovenous Malformation Feeder Vessels With and Without Aneurysms. Stroke. 2015 Jul;46(7):1997–9.

24 Cagnazzo F, Brinjikji W, Lanzino G. Arterial aneurysms associated with arteriovenous malformations of the brain: classification, incidence, risk of hemorrhage, and treatment-a systematic review. Acta Neurochir (Wien). 2016 Nov;158(11):2095–104.

25 Pollock BE, Flickinger JC, Lunsford LD, Bissonette DJ, Kondziolka D. Factors that predict the bleeding risk of cerebral arteriovenous malformations. Stroke. 1996 Jan;27(1):1–6.