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Authors

Abla, Adib A
Nelson, Jeffrey
Kim, Helen
et al.

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Silent Arteriovenous Malformation Hemorrhage and the Recognition of "Unruptured" Arteriovenous Malformation Patients Who Benefit From Surgical Intervention

Adib A. Abla, MD[*], **Jeffrey Nelson, MS**[‡], **Helen Kim, PhD**[‡], **Christopher P. Hess, MD, PhD**[§], **Tarik Tihan, MD**[¶], and **Michael T. Lawton, MD**[*,‡]

[*]Department of Neurological Surgery, University of California, San Francisco, San Francisco, California

[‡]Department of Anesthesia and Perioperative Care, Center for Cerebrovascular Research, University of California, San Francisco, San Francisco, California

[§]Department of Radiology, University of California, San Francisco, San Francisco, California

[¶]Department of Pathology, University of California, San Francisco, San Francisco, California

Abstract

BACKGROUND—Arteriovenous malformation (AVM) patients present in 4 ways relative to hemorrhage: (1) unruptured, without a history or radiographic evidence of old hemorrhage (EOOH); (2) silent hemorrhage, without a bleeding history but with EOOH; (3) ruptured, with acute bleeding but without EOOH; and (4) reruptured, with acute bleeding and EOOH.

OBJECTIVE—We hypothesized that characteristics and outcomes in the unrecognized group of silent hemorrhage patients may differ from those of unruptured patients.

METHODS—Two hundred forty-two patients operated-on since 1997 were categorized by hemorrhage status and hemosiderin positivity in this cohort study: unruptured (group 1), silent hemorrhage (group 2), and ruptured/reruptured (group 3/4). Group 3/4 was combined because hemosiderin cannot distinguish acute hemorrhage from older silent hemorrhage.

RESULTS—Hemosiderin was found in 45% of specimens. Seventy-five patients (31.0%) had unruptured AVMs, 30 (12.4%) had silent hemorrhage, and 137 (56.6%) had ruptured/ reruptured AVMs. Deep drainage, posterior fossa location, preoperative modified Rankin Scale (mRS) score, outcome, and macrophage score were different across groups. Only the macrophage score was different between the groups without clinical hemorrhage. Outcomes were better in silent hemorrhage patients than in those with frank rupture (mean mRS scores of 1.2 and 1.7, respectively).

Correspondence: Michael T. Lawton, MD, University of California, San Francisco, Department of Neurological Surgery, 505 Parnassus Avenue, M780, San Francisco, CA 94143. lawtonm@neurosurg.ucsf.edu.

Disclosures

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CONCLUSION—One-third of patients present with silent AVM hemorrhage. No clinical or anatomic features differentiate these patients from unruptured patients, except the presence of hemosiderin and macrophages. Silent hemorrhage can be diagnosed using magnetic resonance imaging with iron-sensitive imaging. Silent hemorrhage portends an aggressive natural history, and surgery halts progression to rerupture. Good final mRS outcomes and better outcomes than in those with frank rupture support surgery for silent hemorrhage patients, despite the findings of ARUBA.

Keywords

Arteriovenous malformation; Cerebral microbleed; Hemorrhage; Hemosiderin; Silent AVM hemorrhage; Silent intralesional microhemorrhage

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ARUBA (A Randomized trial of Unruptured Brain Arteriovenous malformations) has already had a dramatic impact on the management of unruptured arteriovenous malformations (AVMs) around the world. The 109 patients assigned to medical management had a threefold lower incidence of stroke or death (10.1%) than the 114 patients assigned to interventional therapy (30.7%), which consisted of embolization (32%), radiosurgery (33%), embolization plus radiosurgery (16%), or surgery (18%). Based on this difference, the Data Safety and Monitoring Board stopped patient recruitment after 33 months. Some clinicians have interpreted ARUBA as a moratorium on elective intervention for unruptured AVMs, but this interpretation would deprive some patients of safe and effective intervention, namely, those with low-grade AVMs (Spetzler-Martin grades I and II) that fare well with surgery and those with silent AVM hemorrhage that are at increased risk of future hemorrhage.

Brain AVMs are often characterized dichotomously as unruptured or ruptured, based on a patient's clinical presentation with symptoms, signs, or radiological findings of hemorrhage. Symptoms and signs of rupture consist of seizure, altered mental status, and/or new neurological deficits, whereas computed tomography (CT) scans and magnetic resonance imaging (MRI) demonstrate acute blood in adjacent parenchyma, ventricles, or subarachnoid spaces. The importance of this dichotomy is evident in studies like ARUBA[1] and SIAVMs (Scottish Audit of Intracranial Vascular Malformations),[2] but this characterization may be too simplistic. Like aneurysms, AVMs may also have an intermediate condition that precedes frank rupture with a small warning leak or "sentinel hemorrhage." The sentinel hemorrhage associated with aneurysms is well-known, characterized by sudden, severe headache, described by patients as a "thunderclap" headache and the "worst headache of my life," with intensity off the pain scale. The amount of bleeding is sometimes undetectable on CT scans but is present in cerebrospinal fluid obtained with lumbar puncture. AVMs likely have small hemorrhages as well, but this clinical entity has not been characterized because, unlike with aneurysms, they are clinically silent, often without even a headache. The amount of bleeding is small and has been labeled "microhemorrhage."[3] Bleeding is typically contained intralesionally, but can extend extralesionally into adjacent parenchyma.[3] Over time, leaks deposit hemosiderin in surrounding tissue and induce inflammation, gliosis, and scarring.[3] These changes may trigger seizures and lead to patient presentation, clinical

evaluation, and radiographic diagnosis of the AVM, often remote in time from the bleeding event, contributing to the misconception that the AVM has not bled.[3]

In a previous report, our group documented evidence of silent AVM hemorrhage, which we described as silent intralesional microhemorrhage.[3] In a cohort of 975 AVM patients with CT and/or MRI, 63 patients (6.5%) had evidence of old hemorrhage (EOOH), defined as imaging evidence of bleeding before AVM diagnosis or hemorrhage symptoms. MRI evidence consisted of signal loss from hemosiderin, encephalomalacia adjacent to the lesion, and parenchymal calcifications, whereas CT evidence consisted of encephalomalacia and parenchymal calcifications.[3] We also previously demonstrated hemosiderin positivity in 46 of 127 AVM samples from surgical resections (36.2%).[3] This study showed that silent intralesional microhemorrhage was a risk factor for later AVM rupture. Both EOOH (odds ratio [OR]: 3.97, $P < .001$) and hemosiderin positivity (OR: 3.64, $P = .034$) were highly predictive of index intracerebral AVM hemorrhage.[3]

Based on these findings, AVM patients present in 4 ways, not 2, relative to AVM hemorrhage: (1) unruptured, without a history or radiographic EOOH; (2) silent hemorrhage, without a bleeding history but with radiographic EOOH; (3) ruptured, with acute bleeding but without radiographic EOOH; and (4) reruptured, with acute bleeding and radiographic EOOH. The first group is the classic unruptured AVM patient examined in ARUBA, whereas the third group is the classic ruptured AVM patient excluded from ARUBA. The second group with silent hemorrhage is clinically unruptured and, according to ARUBA, should be observed, but they are at increased risk of bleeding or progressing to the fourth group (Figure 1A). At odds with ARUBA, these silent hemorrhage patients might benefit from intervention, and therefore should be distinguished from other unruptured AVM patients.

In the current study, we analyzed a surgical cohort of 242 AVM patients according to these different presentations to better define features associated with this unrecognized subgroup of unruptured AVM patients with silent hemorrhage. We hypothesized that good outcomes can be achieved in this group of patients with intervention and that clinical characteristics might distinguish the silent subgroup of unruptured AVM patients.

METHODS

Study Design and Setting

This study was approved by the University of California Institutional Review Board and performed in compliance with Health Insurance Portability and Accountability Act regulations. Patients with brain AVMs were identified from 2 prospectively maintained databases: (1) the University of California, San Francisco Brain AVM Study Project and (2) the University of California, San Francisco Neuropathology AVM database. Patients who underwent AVM surgery since September 1997 were included in this study if their tissue sample contained incorporated brain matter and at least a single artery and the patient was present in both databases. Demographic information, hemosiderin and macrophage scores, components of the Spetzler-Martin[4] and Lawton-Young grading systems,[5] AVM location, mode of presentation, and outcomes measured by the modified Rankin Scale (mRS), were

collected from the databases. Additional data, such as operative reports, intraoperative photographs, and radiographic images, were reviewed retrospectively. Radiographic outcome was assessed with postoperative angiography performed in all patients after microsurgical resection. Patient outcome evaluations were performed by a neurologist or trained study coordinator during postoperative clinic visits. Patients missing Spetzler-Martin grades, Lawton-Young grades, or surgical outcome information were excluded from the analyses (Figure 1B).

Patient Groups

Patients were categorized into groups based on whether they had clinical evidence of hemorrhage before resection. Patients with “unruptured” AVMs were further subdivided into unruptured AVM patients (group 1) with no clinical history of hemorrhage and no hemosiderin in or around the AVM specimen and silent AVM hemorrhage patients (group 2) with no clinical history of hemorrhage but with hemosiderin in or around the AVM specimen. Patients with ruptured (group 3) and reruptured (group 4) AVMs were difficult to differentiate because acute hemorrhage produces hemosiderin positivity within 5 to 7 days, often before AVM resection.

Therefore, ruptured AVM specimens from group 4 patients might be hemosiderin positive from a previous silent hemorrhage (true group4 patients) or might be hemosiderin positive from delayed surgery (false group 4 patients). Histopathological analysis cannot distinguish the hemosiderin due to acute hemorrhage and delayed surgery from the hemosiderin due to old silent hemorrhage. Therefore, ruptured and reruptured AVMs patients were combined into a single group (group 3/4) with a clinical history of hemorrhage, regardless of hemosiderin positivity.

Neuroradiology Variables Studied

A subspecialty-certified neuroradiologist blinded to patient history (C.H.) reviewed available preoperative MRI and CT in 37 cases of silent AVM hemorrhage for those imaging features that identify such cases pre factum. Imaging characteristics of interest included signal loss on MRI from hemosiderin or other EOOH, including encephalomalacia adjacent to the lesions or parenchymal calcification. Similarly, CT EOOH consisted of encephalomalacia and parenchymal calcifications.[3]

Histopathology Variables Studied

Two neuropathologists blinded to patient history analyzed hematoxylin and eosin–stained sections for the amount of hemosiderin on a 5-point scale, using birefringence or brownish material in vascular wall or stromal tissue and between vascular elements as criteria for hemosiderin positivity. Each neuropathologist reviewed all samples to ensure consistency and agreement of hemosiderin grading to reduce bias. Previously, we reported hemosiderin positivity as none, small, moderate, or large.[3] Here we characterize hemosiderin positivity on a grading scale from 0 to 4, where 0 indicates no hemosiderin and 1 through 4 indicate minimal, focal, marked, or extensive, respectively. Macrophage infiltration was also graded on a 5-point scale (none, minimal, focal, marked, or extensive), as previously reported.[3]

Specimens were considered positive for hemosiderin or macrophage if the corresponding score was ≥1.

Statistical Analysis

We tested for differences in demographic and clinical features across the 3 patient groups (group 1, group 2, and group 3/4). When the overall comparison was statistically significant, we performed a post hoc comparison of the 2 groups with no clinical evidence of hemorrhage (group 1 and group 2). Categorical variables, such as the presence of deep venous drainage, were compared with the Fisher exact test (or χ^2 test). Continuous variables, such as AVM size, were compared with analysis of variance. We tested whether patient group was a predictor of surgical outcome independent of Spetzler-Martin grade and logarithmic time from resection to follow-up using a likelihood ratio test comparing with a logistic regression model without patient group. We calculated the hemosiderin's positive predictive value of clinical hemorrhage. We calculated the nonparametric correlation (Spearman's ρ) of hemosiderin and macrophage using the 0 to 4 scores. We calculated the frequency of radiographic features from a secondary neuroradiology data set of 37 silent hemorrhage patients. $P < .05$ were considered statistically significant. All analyses were performed with Stata/SE version 13.1 (StataCorp, College Station, Texas).

RESULTS

Characterization of Silent AVM Hemorrhage and Patient Descriptive Data

Our sample included 242 patients. Silent AVM hemorrhage patients (group 2) made up a minority of the sample (30, 12.4%), far fewer than the number of patients with unruptured AVMs (group 1, 75 patients, 31.0%) and ruptured/reruptured AVM patients (group 3/4, 137 patients, 56.6%) (Table). Of the 105 patients without a clinical history of AVM hemorrhage, 28.6% had silent hemorrhages. Patients with silent AVM hemorrhage presented with seizures 40% of the time, and unruptured patients presented with seizures 44% of the time; this difference was not significant ($P = .828$).

Silent AVM hemorrhage patients had an incidence of deep venous drainage that was more like unruptured AVM patients (33% for both groups 1 and 2), which was significantly lower than patients presenting with AVM rupture or rerupture (55% for group 3/4; $P < .001$) (Table and Figure 2A). AVM size, eloquence, and Spetzler-Martin grade were not significantly different between groups. There were no significant differences in patient age and compact nidus, but the Lawton-Young grades were approximately 1 point lower in patients with ruptured/reruptured AVMs because this supplementary grading system incorporates AVM hemorrhage ($P < .001$). Ruptured/reruptured AVMs were more frequently located in the posterior fossa compared with unruptured AVMs and those with silent hemorrhage ($P = .008$; Figure 2B); however, there was no observed difference between group 1 and group 2 ($P = .389$).

Outcome Data

Silent AVM hemorrhage patients presented in good neurological condition, with baseline mRS scores similar to those of unruptured AVM patients (Table and Figure 2C). These

baseline mRS scores were significantly better than the scores of patients with ruptured/reruptured AVMs ($P < .001$), reflecting the different neurological impact of microhemorrhage compared with frank rupture. Patients presenting with ruptured/reruptured AVMs (group 3/4) improved neurologically at their first and last postoperative evaluations, relative to baseline, indicating their compromised condition at presentation and recognized benefits of hemorrhage and hematomas in circumdissecting and resecting AVMs. In contrast, patients presenting with unruptured AVMs (groups 1 and 2) deteriorated after surgery, indicating the morbidity associated with resecting AVMs in patients with incidental lesions, seizures, and/or no preoperative deficits ($P = .001$). However, there were no significant differences in neurological deterioration after surgery in patients with unruptured AVMs and those with silent AVMs ($P = .252$), indicating that microhemorrhage did not confer any measurable benefits in circumdissection and resection, as it does with frank rupture. At last follow-up, mRS outcomes were better in silent AVM hemorrhage patients whose AVMs were resected before frank rupture than in those who experienced frank rupture, with mean mRS scores of 1.2 and 1.7 in group 2 and group 3/4, respectively.

A more sophisticated logistic regression analysis that factored in short recovery times and high Spetzler-Martin grades as predictors of a worsening of mRS score after surgery yielded similar results: patient group was a significant predictor of poor outcome(likelihood ratio test, $P < .001$), but a comparison of groups 1 and 2 found no difference ($P = .109$).

Main Results: Hemosiderin Positivity and Macrophage Infiltration

Hemosiderin positivity was the definitive marker of silent hemorrhage and was found in 45% of AVM specimens (110 of 242). It was present in 29% of patients with unruptured AVMs (30 of 105) and in 58% of patients with ruptured AVMs (80 of 137) ($P < .001$). Its positive predictive value for clinically symptomatic hemorrhage was 73% (80 of 110).

Macrophage infiltration was found in 51% of AVM specimens overall (123 of 242) and was present in 13% of unruptured AVMs, 90% of AVMs with silent hemorrhage, and 63% of ruptured/reruptured AVMs ($P < .001$). Of all the demographic and clinical features analyzed, apart from hemosiderin positivity that defined patient groups, macrophage infiltration was the only feature that significantly differentiated AVMs with silent hemorrhage from unruptured AVMs ($P < .001$) (Table). Hemosiderin scores and macrophage infiltration scores were very strongly correlated ($P < .001$, Spearman ρ coefficient ($r = 0.822$) (Figure 3).

Main Results: Radiographic Features

Radiographic evidence of 30 silent AVM hemorrhages in group 2 consisted of hemosiderin in 6 of 19 patients (31.2%) who underwent preoperative MRI, encephalomalacia in 7 of 22 patients (31.8%) who underwent preoperative MRI and/or CT, calcifications in 8 of 17 patients (47.1%) who had preoperative CT, and T2 signal in 12 of 19 patients (63.2%). Two illustrative cases of patients with silent AVM hemorrhage demonstrate the radiographic findings and intraoperative gross appearance of the AVM and adjacent brain intraoperatively (Figure 4).

DISCUSSION

Key Results

This report defines and characterizes the clinical entity of silent AVM hemorrhage. Patients with silent AVM hemorrhage (group 2) are typically categorized as having unruptured AVMs because they have no hemorrhagic symptoms or history. Based on the findings of ARUBA and other studies, these patients might be managed with conservative observation.[1,2] However, patients with silent hemorrhage likely have a more dangerous natural history than truly unruptured AVM patients (group 1). In our previous report, EOOH on CT scans or MRI was highly predictive of hemorrhagic presentation (OR: 3.97, 95% confidence interval: 2.1–7.5, $P < .001$) and was an independent predictor of new hemorrhage in the natural history course (hazard ratio: 3.53, 95% confidence interval: 1.3–9.2, $P = .01$).[3] Furthermore, hemosiderin positivity was independently associated with hemorrhagic presentation (OR: 3.64, 95% confidence interval: 1.1–12.0, $P = .03$) in 79 AVM patients.[3] Our current study extends these findings to clinical characteristics and outcomes after resection. We found no symptoms or signs, and no clinical or anatomic features that differentiate patients with silent hemorrhage from those with unruptured AVMs. We observed no difference in outcome after surgery in the silent AVM hemorrhage group compared with the unruptured AVM group. However, hemosiderin positivity was strongly associated with macrophages, suggesting that AVMs with silent hemorrhage are more biologically active and inflamed lesions. These findings are consistent with the significantly higher risk of subsequent hemorrhage in silent hemorrhage patients than in unruptured AVM patients.

Management Implications

These findings are critically important in the ARUBA aftermath because they suggest that silent hemorrhage patients should be managed more aggressively than unruptured AVM patients. Although it may be appropriate to recommend conservative observation to the latter unruptured AVM group, therapeutic intervention should be considered in the former silent hemorrhage group, particularly those patients with long life expectancy and acceptably low treatment risks, as with low-grade AVMs. These group 2 patients represent 29% of patients without a clinical history of bleeding and 12% of the overall cohort. Our study demonstrates the need to establish the diagnosis of silent AVM hemorrhage and manage these patients differently.

Interpretation: The Diagnosis of Silent AVM Hemorrhage

Clinically silent microhemorrhage from AVMs has been recognized by neurosurgeons who encounter hemosiderin-stained parenchyma, gliosis, and encephalomalacia adjacent to the nidus during circumdissection in patients without hemorrhagic symptoms.[3,6] However, the syndrome of silent AVM hemorrhage was not relevant until imaging provided techniques to identify the presence of microhemorrhage in asymptomatic patients. CT scanning offers limited sensitivity to the presence of subacute or remote hemorrhage and is better instead for detecting evidence of more significant and destructive previous hemorrhages (eg, encephalomalacia). In contrast, MRI, especially with iron-sensitive imaging sequences such as gradient echo T2* and more recently developed techniques for susceptibility-sensitive

imaging such as susceptibility-weighted imaging, is exquisitely sensitive for detecting AVM microhemorrhage.[7,8] As early as 1993, Prayer et al[9] demonstrated that T1- and T2-weighted MRI detected blood breakdown products and hemosiderin in 20% of AVM patients who had no clinical symptoms of hemorrhage. Susceptibility-sensitive techniques further improve MRI sensitivity to microhemorrhage, and the availability of machines with high magnetic field strengths (3 and 7 T) will further increase the diagnosis of silent AVM hemorrhage.[10] Advanced imaging technology has identified cerebral microbleeds seen in association with other disease processes in addition to AVMs, such as aneurysmal subarachnoid hemorrhage, moyamoya disease, amyloid angiopathy, Alzheimer disease, postradiation injury, and endovascular intervention, leading to more than 400 publications on the topic over the past 4 years.[11–27]

Silent AVM hemorrhage is largely an imaging diagnosis because of the small volume of blood degradation products, intralesional location, and absence of clinical symptoms.[3] However, presentation with seizures should raise the index of suspicion and trigger evaluation with MRI. Our previous study demonstrated that conventional MRI detects silent AVM hemorrhage in only 6.5% of patients,[3] and the current study demonstrates that the true incidence of hemosiderin positivity in resected AVM specimens is as high as 45% overall and 29% in unruptured patients. Therefore, the MRI evaluation of unruptured AVM patients must include modern susceptibility-sensitive sequences to improve detection rates.

Our study demonstrated a significant correlation between hemosiderin positivity and macrophage infiltration (Figure 3) ($P < .001$). Both measures are based on pathological analysis and are impractical clinical tests, but like hemosiderin positivity that can be imaged with susceptibility-sensitive MRI, macrophage infiltration can be imaged by administering ferumoxytol, an ultrasmall superparamagnetic iron oxide that is ingested by macrophages and other inflammatory cells associated with silent AVM hemorrhages.[28] Iron-sensitive imaging sequences of MRI then identify ferumoxytol-laden macrophages around an AVM by comparing images obtained before and 5 days after administration of the agent. The combination of special imaging techniques for hemosiderin and macrophages is expected to increase the diagnosis of silent hemorrhage in unruptured AVM patients and is the subject of ongoing investigation.

Interpretation: Surgical Considerations

At our institution, surgical resection with or without adjunctive embolization is considered the gold standard therapy for AVMs, and therefore our findings support a new surgical indication. Although there are important radiographic and natural history differences between patients with unruptured AVMs and those with silent hemorrhage, we found no significant differences in their outcomes after surgery. Although silent hemorrhage induces inflammation, gliosis, and scarring in adjacent parenchyma that helps to develop the dissection plane around an AVM, it does not create the same surgical benefits as frank rupture, which can separate the margins of the nidus from the brain, create nonanatomic routes of access to deep lesions, open cavities of working space after hematoma evacuation, and dramatically alter the surgical risk profile by producing neurological deficits at presentation. Silent AVM hemorrhage patients typically present intact neurologically, and

therefore they are more likely to remain unchanged or be slightly worse after surgery, like the classic unruptured AVM patient. Therefore, the neurosurgeon should be judicious with patient selection and not expect to find the surgical advantages associated with AVM rupture. Still, final outcomes in patients with silent AVM hemorrhage are excellent (mean last mRS score, 1.2) and better than in those who experience frank rupture (mean last mRS score, 1.7), indicating that surgery preventing frank rupture in silent AVM hemorrhage patients may be beneficial and that management with a more interventional posture than would otherwise be suggested by ARUBA is appropriate. The devastating effects of frank rupture were evident in group 3/4 patients and emphasize the importance of managing patients with silent AVM hemorrhage aggressively to protect them from their more dangerous natural history, instead of being managed conservatively in the ARUBA aftermath.

Limitations and Generalizability

Clinical results reported herein may not be generalizable outside of a tertiary center that treats a high volume of AVMs with surgery. Additionally, the patients and AVMs may be younger and more aggressive or complex than are seen in a general neurosurgical practice. Although patients were included prospectively in the database registries, overall study design, statistical analyses, and patient groups, as well as inclusion criteria for this study, were developed post hoc after prospective patient enrollment.

CONCLUSION

Nearly one-third of patients without a clinical history of AVM hemorrhage had hemosiderin on surgical pathology, indicating silent AVM hemorrhage. We found no symptoms or signs and no clinical or anatomic features that differentiate patients with silent AVM hemorrhage from those with unruptured AVMs. Hemosiderin and macrophages were the only features that differentiate these patients, making silent AVM hemorrhage an entirely radiological diagnosis. This diagnosis is possible pre factum, without knowledge of surgical pathology findings, using available MRI sequences with iron-sensitive imaging and ferumoxytol. Silent AVM hemorrhage portends a more aggressive natural history and a real threat of hemorrhage, and surgery can halt progression from silent AVM hemorrhage to rerupture. Good final mRS outcomes in silent AVM hemorrhage patients and better outcomes than in those with frank rupture support surgical management of silent AVM hemorrhage patients, despite the findings of ARUBA.

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ABBREVIATIONS

AVM	arteriovenous malformation
EOOH	evidence of old hemorrhage

mRS modified Rankin Scale

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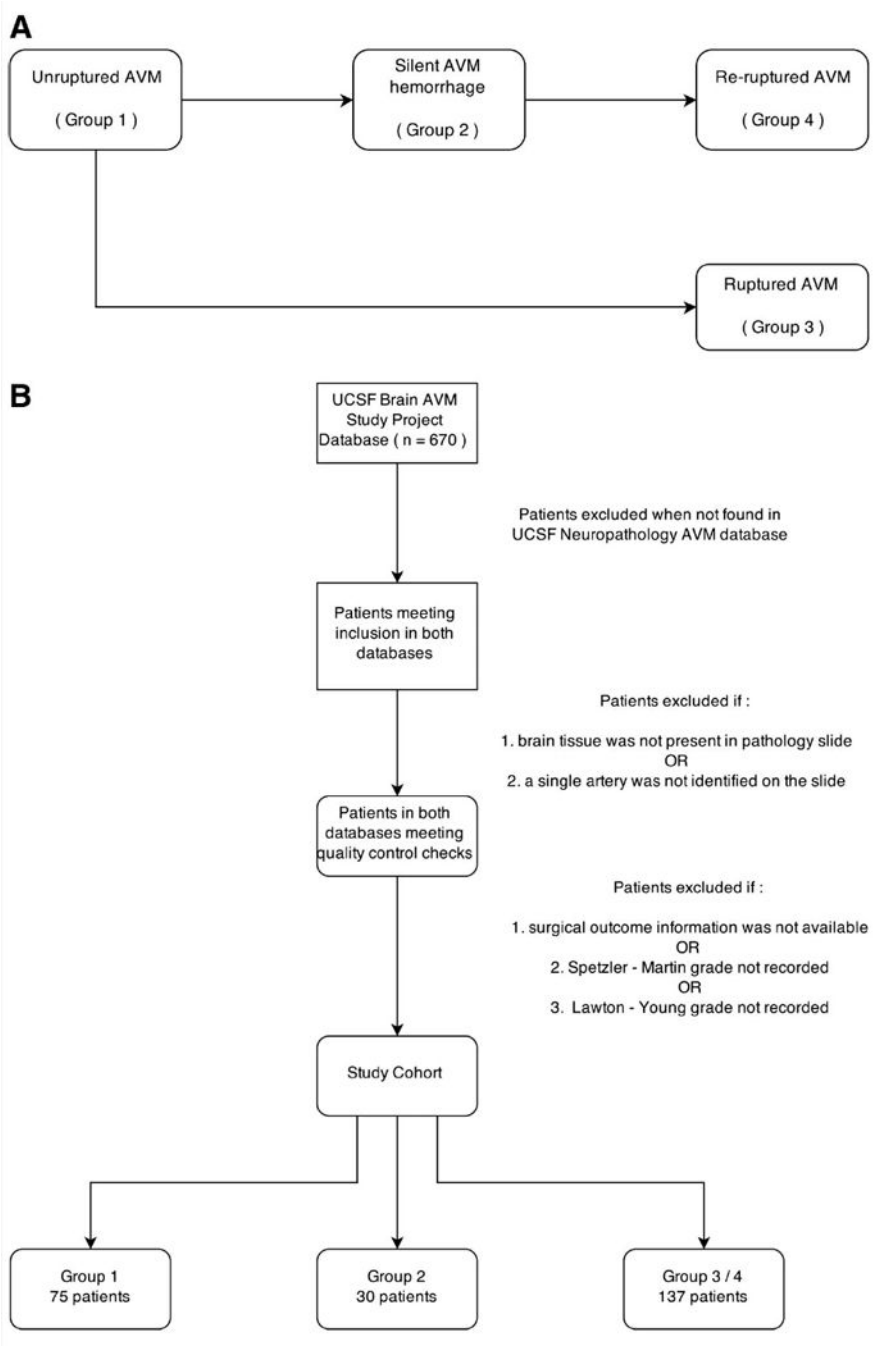

FIGURE 1.

A, progression of arteriovenous malformations (AVMs) from unruptured AVM to ruptured AVM. AVM patients present in 4 ways, relative to AVM hemorrhage: unruptured, without a history or radiographic evidence of hemorrhage (group 1); silent hemorrhage, without a bleeding history but with radiographic evidence of old hemorrhage (EOOH) (group 2); ruptured, with acute bleeding but without radiographic EOOH (group 3); and reruptured, with acute bleeding and radiographic EOOH (group 4). The first group is the classic unruptured AVM patient; the third group is the classic ruptured AVM patient; the second

group with silent hemorrhage is clinically unruptured but has increased risk of bleeding or progressing to the fourth group. **B**, inclusion and exclusion criteria for patients in this cohort. UCSF, University of California, San Francisco.

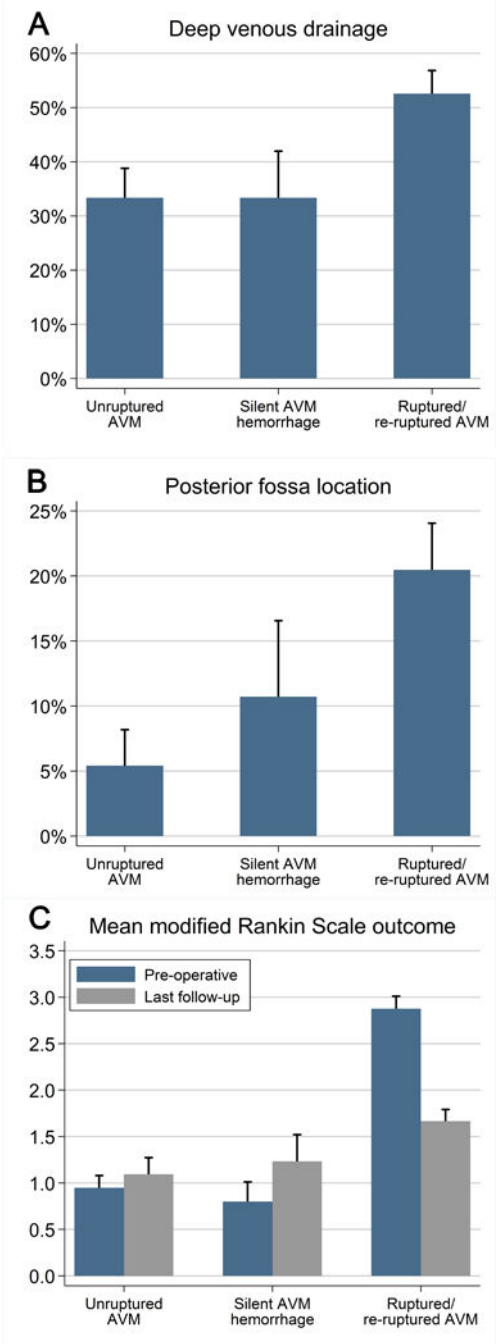

FIGURE 2.

Comparison of deep venous drainage (**A**) (P = .012), posterior fossa location (**B**) (P = .008), and mean modified Rankin Scale (mRS) score preoperatively and at last follow-up (**C**) (P < .001 and P = .487, respectively). AVM, arteriovenous malformation.

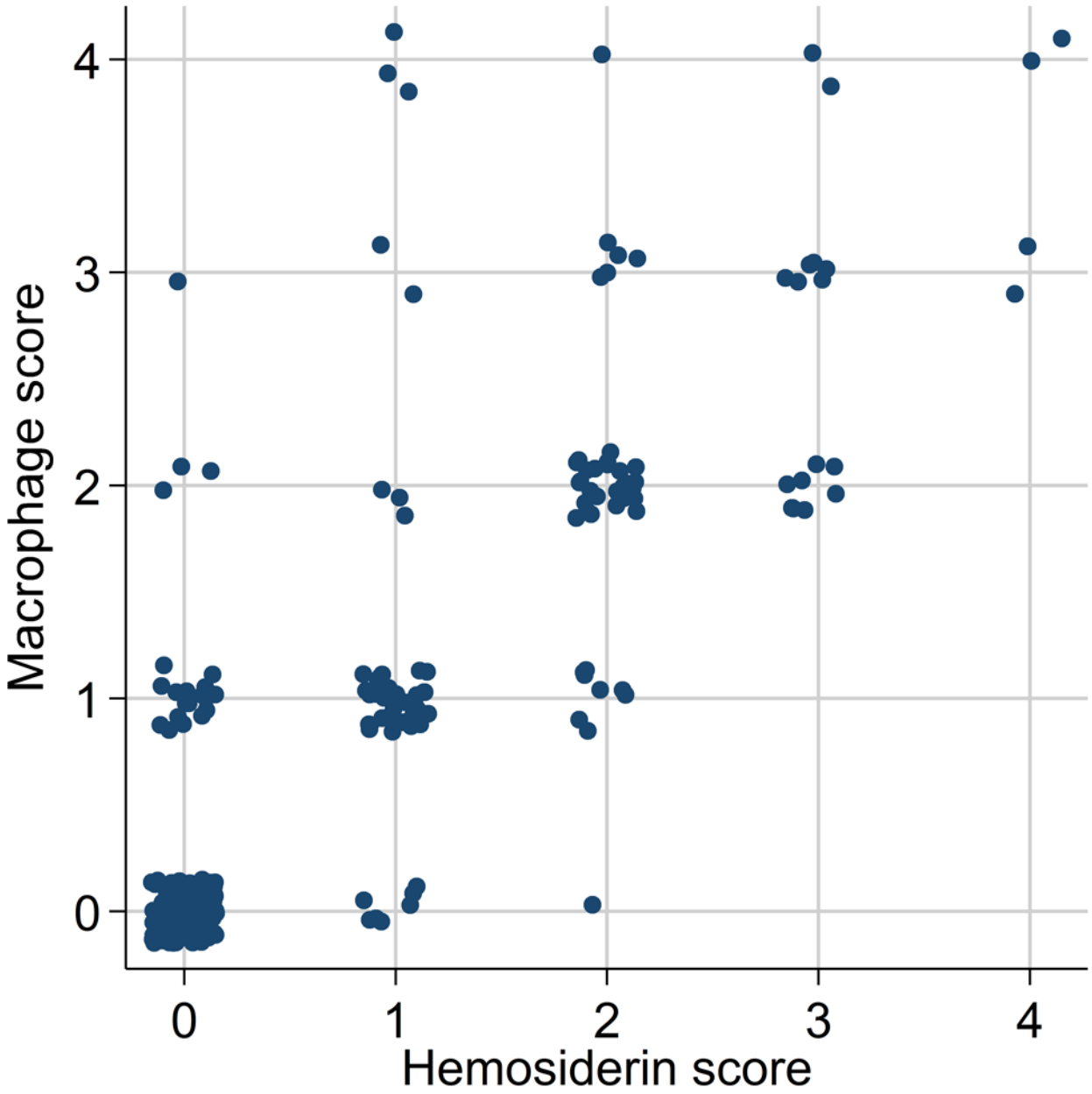

FIGURE 3.
Correlation of hemosiderin score with macrophage score: Spearman coefficient $r = +0.822$ ($P < .001$).

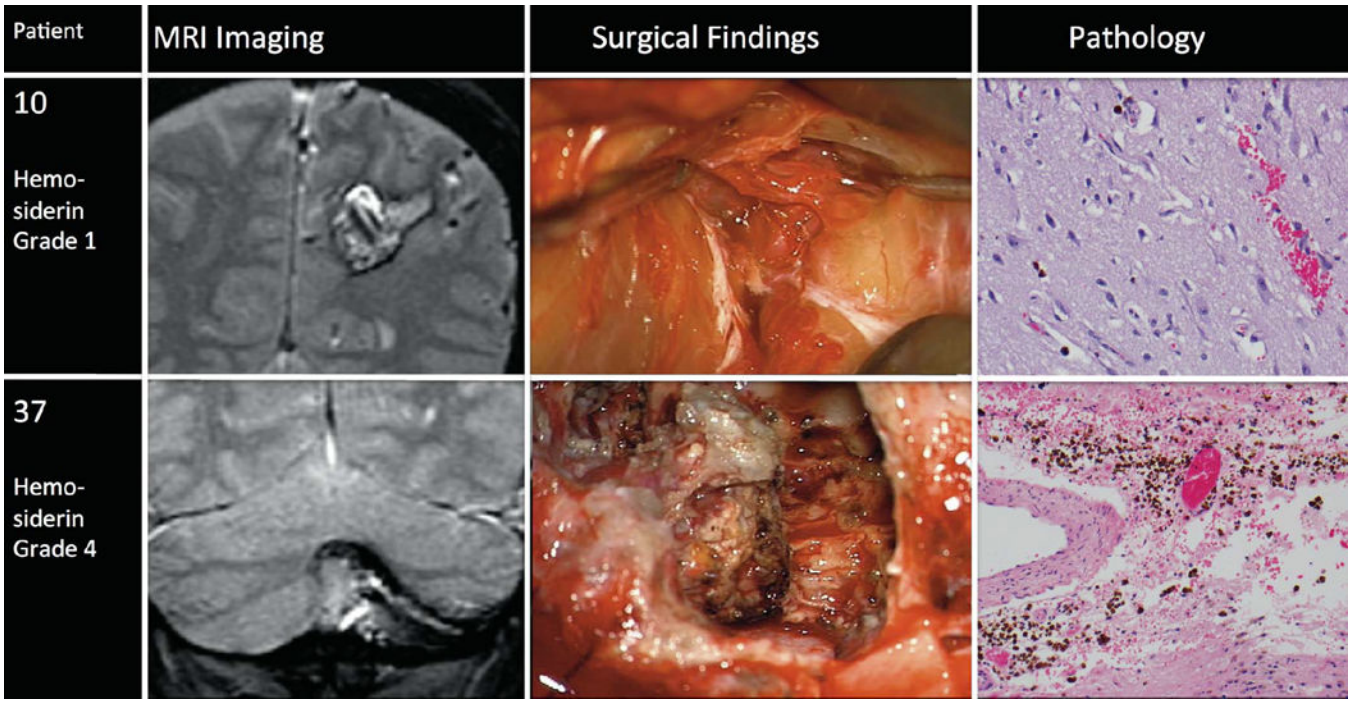

FIGURE 4.

Two case examples illustrating preoperative coronal magnetic resonance imaging (MRI) with T2-weighted imaging, intraoperative photos, and pathological specimens (hematoxylin and eosin staining), one showing minimal scattered hemosiderin pigment and the other abundant hemosiderin (original magnification ×200).

TABLE

Demographic and Clinical Characteristics of 242 AVM Patients[a]

	Group 1 Unruputured	Group 2 Silent Hemorrhage	Group 3/4 Ruptured/Reruptured	*P* Value	
				All Groups	Group 1 vs 2
Characteristic	n = 75	n = 30	n = 137		
Female sex	34 (45)	16 (53)	65 (47)	.768	
Seizures at presentation	33 (44)	12 (40)	17 (12)	<**.001**	.828
AVM size, cm	3.00 ± 1.14	2.88 ± 1.30	2.72 ± 1.34	.290	
Deep venous drainage	25 (33)	10 (33)	72 (52)	**.012**	1.000
Eloquence	39 (52)	11 (37)	82 (60)	.060	
Spetzler-Martin grade				.332	
1	15 (20)	9 (30)	19 (14)		
2	29 (39)	9 (30)	45 (33)		
3	22 (29)	7 (23)	51 (37)		
4	9 (12)	5 (17)	19 (14)		
5	0 (0)	0 (0)	3 (2)		
Age at resection, y	37.8 ± 15.2	42.2 ± 12.6	36.2 ± 18.4	.199	
Diffuse AVM	10 (13)	6 (20)	24 (18)	.641	
Lawton-Young grade				<**.001**	.482
1	0 (0)	0 (0)	21 (15)		
2	7 (9)	1 (3)	48 (35)		
3	31 (41)	10 (33)	53 (39)		
4	33 (44)	16 (53)	13 (9)		
5	4 (5)	3 (10)	2 (1)		
Posterior fossa location[b]				**.008**	.389
Yes	4 (5)	3 (11)	26 (20)		
No	70 (95)	25 (89)	101 (80)		
mRS score ≥ 3 before resection	8 (11)	2 (7)	90 (66)	<**.001**	.528
mRS score ≥ 3 at last follow-up	11 (15)	5 (17)	29 (21)	.487	

	Group 1 Unruputured	Group 2 Silent Hemorrhage	Group 3/4 Ruptured/Reruptured	*P* Value	
				All Groups	Group 1 vs 2
Worsening of mRS score	21 (28)	12 (40)	18 (13)	**.001**	.252
Time to last follow-up, y[c]	1.35 ± 1.44	2.45 ± 2.82	1.91 ± 3.00	.130	
Hemosiderin score				n/a	
0: none	75 (100)	0 (0)	57 (42)		
1: minimal	0 (0)	18 (60)	30 (22)		
2: focal	0 (0)	10 (33)	31 (23)		
3: marked	0 (0)	2 (7)	15 (11)		
4: extensive	0 (0)	0 (0)	4 (3)		
Macrophage score				<**.001**	<**.001**
0: none	65 (87)	3 (10)	51 (37)		
1: minimal	8 (11)	18 (60)	32 (23)		
2: focal	2 (3)	7 (23)	32 (23)		
3: marked	0 (0)	2 (7)	14 (10)		
4: extensive	0 (0)	0 (0)	8 (6)		

Values are no. (%) or mean ± standard deviation. *P* values are from Fisher exact test, χ^2 test, or analysis of variance. The first *P* value test for differences across all groups. If the first *P* value was significant, we tested for differences between groups 1 and 2.

[a] AVM, arteriovenous malformation; mRS, modified Rankin Scale.

[b] Posterior fossa location information was not available for all patients.

[c] The analysis of variance for time to last follow-up used log-transformed values.

The bold font indentifies statistically significant values.