Original Article

A proposed classification for assessing rupture risk in patients with intracranial arteriovenous malformations

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Abstract

Background: Whether cerebral arteriovenous malformations (AVMs) should be treated remains an ongoing debate. Nevertheless, there is a need for predictive factors that assist in labelling lesions as low or high risk for future rupture. Our aim was to design a new classification that would consider hemodynamic and anatomic factors in the rapid assessment of rupture risk in patients with AVMs.

Methods: This was a retrospective study that included 639 patients with ruptured and unruptured AVMs. We proposed a new classification score (1–4 points) for AVM rupture risk using three factors: feeding artery mean velocity (Vm), nidus size, and type of venous drainage. We employed descriptive statistics and logistic regression analysis.

Results: A total of 639 patients with cerebral AVMs, 388 (60%) had unruptured AVMs and 251 (40%) had ruptured AVMs. Logistic regression analysis revealed a significant effect of Vm, nidus size, and venous drainage type in accounting for the variability of rupture odds ($P = 0.0001$, $R^2 = 0.437$) for patients with AVMs. Based in the odds ratios, grades 1 and 2 of the proposed classification were corresponded to low risk of hemorrhage, while grades 3 and 4 were associated with hemorrhage: 1 point OR = (0.107 95% CI; 0.061–0.188), 2 point OR = (0.227 95% CI; 0.153–0.338), 3 point OR = (3.292 95% CI; 2.325–4.661), and 4 point OR = (23.304 95% CI; 11.077–49.027).

Conclusion: This classification is useful and easy to use, and it may allow for the individualisation of each cerebral AVM and the assessment of rupture risk based on a model of categorisation.

Key Words: Cerebral arteriovenous malformations, cerebral hemodynamics, Doppler ultrasound, cerebral venous drainage

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INTRODUCTION

The Spetzler and Martin (SM) classification of arteriovenous malformations (AVMs), published in 1986,\textsuperscript{[33]} has been useful in the treatment of brain AVMs, allowing neurosurgeons to evaluate the complexity and morbidity of these vascular lesions and to estimate surgical risk.\textsuperscript{[2,37]} Other AVM classifications have been described, such as Spetzler-Ponce, Lawton’s supplementary system, and the Buffalo and Toronto scores;\textsuperscript{[10,11,28,32,33]} however, none of them considers the risk of AVM bleeding. Several anatomic and hemodynamic factors have been associated with increased risk of AVM bleeding, such as deep venous drainage, single venous drainage, malformation nidus size, prior bleeding, and presence of intranidal aneurysm.\textsuperscript{[12,13]}

The aim of this study is to propose a classification system that allows for an estimation of bleeding risk in patients with cerebral AVMs. This proposed classification may help to differentiate between patients at a high risk of bleeding in need of aggressive management and patients with a low risk of bleeding who would benefit more from conservative treatment.

MATERIALS AND METHODS

This was a retrospective study that analysed 639 patients diagnosed with cerebral AVMs, from 1 March 2006 to 31 October 2015 at the Department of Neuroendovascular Therapy at the Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez in Mexico City. The scientific and ethics committees of our institution approved the conduct of this research. We adhered to the Declaration of Helsinki.

The inclusion criteria were as follows: any patient with a diagnosis of cerebral AVM of any grade according to the Spetzler Martin classification, of any sex or age, a complete medical record and an imaging workup including at least a diagnostic cerebral angiogram and a transcranial Doppler ultrasound (TCD). All patients included underwent a head computed tomography scan, a brain magnetic resonance imaging or both. However, these imaging modalities were not used in the classification.

We included patients with ruptured and unruptured AVMs. The diagnosis of ruptured AVMs was confirmed by a head computed tomography scan performed 1 to 24 h after the onset of clinical symptoms in the patient. In these cases, the cerebral angiograms used for this classification were chosen 2 months after bleeding.

Transcranial Doppler ultrasound

TCD was performed by a single operator (FPV) to measure the state of cerebral circulation in real time, using a Siemens Acuson Antares, premium edition, B©. All patients were measured in both anterior cerebral arteries (A1), the middle cerebral artery (M1), and the posterior cerebral artery (P1). Regardless of their affereces, the major arterial trunks (bilateral A1, M1 and P1) were measured with TCD.

All TCD parameters were evaluated in a previous study, where we measured the Vm, resistance index, pulsatility index, and Reynold’s number to determine the degree of hemodynamic characteristics of the AVMs in normotensive patients. In this study, we observed that the hemodynamic parameters can be summarized in the value of the Vm. In this classification, we included all the main feeding artery Vm. Vm was calculated from the systolic velocity plus two diastolic velocities divided by 3 [Table 1].\textsuperscript{[29,35]}

Digital subtraction angiography

This procedure was performed on an Artis zee/zeego robotic arm angiography system and VB21C Syngo Workplace postprocessing stations (Siemens Erlangen, Germany©). The size of the malformation nidus was determined by employing DSA in the measurement of the largest diameter of the AVM nidus and the patterns of venous drainage from the AVM (described below).

Description of the proposed AVM classification system

Three independent variables of all AVMs were analysed: afferent pedicles (measured by mean velocities), nidus size, and efferent vessels (venous drainage). Initially

| Mean Velocity cm/seg | Total patients (n=188) | Bleed (n=111) | Not bleed (n=77) | P | Odds ratio |
|----------------------|------------------------|--------------|-----------------|---|------------|
| <50                  | 6                      | 5            | 1               |   | NS         |
| <60                  | 14                     | 10           | 4               | 0.015 | 4.8 (CI: 1.2-18.7) |
| <70                  | 18                     | 13           | 5               | 0.002 | 6.1 (CI: 1.7-21) |
| <80                  | 33                     | 20           | 13              | 0.001 | 6.7 (CI: 1.9-25) |
| <90                  | 37                     | 21           | 16              | 0.004 | 6.5 (CI: 1.6-26.6) |
| <100                 | 39                     | 21           | 18              | 0.014 | 5 (CI: 1.2-20.5) |
| <110                 | 41                     | 21           | 20              | 0.041 | NS         |

Ns: No significant, CI: Confidence intervals
we analyzed the odds ratios of AVM bleeding from all the range of Vm (each analysis was stratified in 10 cm/s, e.g. 10–19 cm/s) afferent pedicles and nidus size (each cm) to obtain the highest odds ratios related to ruptured AVMs. Then we chose the dichotomous (Vm > or < 90 cm/s) and nidus size (≥ or < 3 cm) or categorical variables (venous drainage type) to be included in the regression model. Venous drainage was categorised according to the venous patterns found in the cerebral angiograms.

The cut-off mean velocities of the main feeding artery were obtained from a previous analysis conducted by our group in which we estimated the odds ratio of bleeding in patients with different categorical Vm values. According to these results, a Vm < 90 cm/s is a risk factor for hemorrhage (OR = 6.5, 95% CI = 1.6, 26.6) compared to a Vm ≥ 90 cm/s (OR = 0.51, 95% CI = 0.34, 0.792) in the principal feeder of the AVM.

The second variable was the malformation nidus size; a nidus < 3 cm (OR = 4.15, 95% CI = 1.29–13.3) had a risk 4-fold higher than a nidus ≥ 3 cm (OR = 0.55, 95% CI = 0.34, 0.89).

The third variable was venous drainage, which behaves differently in each AVM. Based on visual angiographic cerebral AVMs in the present study (cf. infra), we classified the AVMs according to venous drainage behaviour, dividing them into three types with several subtypes.

**Type 1 venous drainage: Anterograde (downstream or normal flow)**

Anterograde venous drainage was considered normal venous drainage, where the region above the superficial sylvian vein drains (either by cortical veins or the vein of Trolard) to the superior sagittal sinus; below the superficial sylvian vein, the flow is directed toward the vein of Labbé, draining into the transverse sinus.

1A) Superficial venous drainage
1B) Superficial and deep venous drainage
1C) Deep venous drainage

[Figure 1]

In this type, we consider the Sylvian fissure to be a natural barrier. Lesions tend to drain away from the superficial sylvian vein, either from the superficial sylvian vein to the superior sagittal sinus or from the superficial sylvian vein to Labbé and the transverse sinus.

**Type 2 venous drainage: Retrograde (upstream or reverse flow)**

Upstream drainage from the skull base to the superior sagittal sinus and/or downstream venous drainage to the contralateral hemisphere from the superior sagittal sinus toward the basal portion.

2A) Superficial and deep venous drainage
2B) Superficial venous drainage

[Figure 2]

In this type, the natural barriers are crossed anti-physiologically; basal lesions drain dorsally, crossing the Sylvian fissure, or hemispherical lesions cross the midline to be drained contralaterally, or convexity lesions drain ventrally, crossing the Sylvian fissure to the skull base.

**Type 3 venous drainage: Retrograde (upstream or reverse flow) + facial venous drainage**

Upstream drainage from the skull base to the Superior sagittal sinus and/or drainage in the downstream contralateral hemisphere from the superior sagittal sinus toward the basal portion associated with facial vein drainage.

3A) Superficial and deep venous drainage
3B) Deep venous drainage

[Figure 3]

*Figure 1* (a) Lateral (A, B) and anteroposterior (AP) (C) cerebral angiogram shows anterograde superficial venous drainage, (downstream) represented in the illustrative image (D). (b) Lateral cerebral angiogram (E, F, G) show mixed venous drainage (superficial and deep), anterograde in which the superficial drainage is represented with red arrows and deep venous drainage with blue arrows in the illustrative image (H). (c) AP (J) and lateral (I, K) cerebral angiogram shows deep venous drainage anterograde (Type 1C), which is shown with blue arrow in the illustrative image (L).
Determination of the grade of cerebral AVM

The proposed classification is calculated from the sum of the points from the three variables; Vm, nidus size, and venous drainage type. Thus, it gives a categorical scale [Figure 4] and the grade is determined by the sum of the points in each category. The minimum score is 1 point, which obtained a lower risk of bleeding and the maximum score is 4 points, which corresponds to a highest risk of bleeding.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and ranges. Initially, we performed the Kolmogorov–Smirnov test for each variable analysed in order to evaluate normality. To define the categories of the afferent pedicles and the nidus size, we calculated the odds ratios (Pearson test) of AVM bleeding in 55 patients and then we established the dichotomous variables of these two parameters.

The significance of baseline differences was determined by the Chi-square test, Fisher’s exact test or the Mann–Whitney U test, as appropriate. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

We used a logistic regression model to estimate the extent and significance to which risk of bleeding of cerebral AVMs is explained by the proposed independent variables (afferent pedicles [measured by mean velocities], nidus size, and efferent vessels [venous drainage]). It is important to clarify that the proposed regression model is phenomenological in the sense that selection of some variables is not directly
derived from theory but rather experimental and empirical observations. The regression model considered as dependent variable presence or absence of ruptured AVM and as independent variables afferent pedicles (measured by mean velocities), nidus size and efferent vessels (venous drainage) reviewed by TCD and digital subtraction angiograms. All the variables were categorical [Figure 4]. SPSS statistical software (version 23) was used.

RESULTS

A total of 639 patients with cerebral AVMs were included and assessed; 321 (50%) males and 318 (50%) females with total mean age of 32.9 (5–82) years.

Sociodemographic findings

The sociodemographic characteristics, comparisons, and odd ratios of our patients according to the presence or absence of brain hemorrhage due to AVMs are summarised in Table 2.

Clinical manifestations

In the group of patients with unruptured AVMs (n = 365), the clinical manifestations at the time of diagnosis were as follows: 202/365 (55.3%) seizures, 164/365 (44.9%) headache, 32/365 (8.7%) seizures, and headache, 30/365 (8.2%) steal phenomena (paresis, paraesthesia, transient amaurosis) and 10/365 (2.7%) were asymptomatic.

The group of patients with ruptured AVMs (n = 274) showed the following symptoms before bleeding: 22/274 (8%) headaches, 9/274 (3.2%) seizures, 2/274 (0.7%) steal phenomena, and 244/274 (89%) were asymptomatic. Table 3 shows the age distribution according to our score.

Figures 5–8 show examples of cerebral AVMs by grade based on our classification.

Logistic regression analysis of bleeding odds in AVMs

On the basis of Chi-square analyses and logistic regression, the influence of sex on bleeding odds was discarded. Nevertheless, Vm, nidus size, and venous drainage type were found to be significant (P = 0.0001). The obtained prediction model of bleeding odds in the context of AVMs is given as: ln (odds) = (-2.248) ·Vm + (-0.878) nidus size + (-0.452) venous drainage. This model allowed for the correct classification of 80.3% of patients without and 77.3% of patients with brain hemorrhage. The logistic regression indicated that anatomic and hemodynamic variables and so the proposed classification explain better the variability of bleeding odds in AVM patients (NR = 621.53, R² = 0.437) as compared to the SM classification (NR = 847.048, R² = 0.053).

The distribution of our patients’ AVMs according to the SM classification was: SM-I: 150 (23.4%); SM-II: 237 (37%); SM-III: 187 (29.2%); SM-IV: 56 (9%) and SM-V: 9 (1.4%). Table 1 shows the odds ratios for each SM score and the 1-4 scores from our classification of cerebral AVM bleeding risk. Interestingly, the AVM bleeding risk increased linearly with the higher values of scores from our proposed classification [Figures 5–8]. SM scores were not associated with the cerebral AVM bleeding risk.

DISCUSSION

The aim in the treatment of an AVM is to prevent future occurrence of intracranial hemorrhage. [1,3,9,12,13,15–18,26,27,30,36,37]
Some studies provide algorithms of AVM treatment based in SM grades; for example, a) surgical treatment for SM grades I and II and only for those grades III cases that are surgically accessible, b) endovascular treatment in patients with lower-grade AVM in patients with comorbidities or palliative in higher grades, c) stereotactic irradiation with Leksell Gamma Knife for complex and deep-seated grade III AVM, and d) observation for IV and V grades.\textsuperscript{1,14,15,20} In the last decade, multiple scales for the classification of different aspects of an AVM have appeared. The SM, Spetzler-Ponce and Lawton’s supplementary classifications\textsuperscript{4,10,11,14,15,32} determine surgical risk and surgical morbidity.\textsuperscript{10} The Buffalo score assesses the risk of developing complications during an endovascular procedure and the Toronto classification predicts the risk of post-surgical morbidity.\textsuperscript{28} However, none of the

Table 2: Sociodemographic characteristics of 639 patients with cerebral AVMs, their distribution in ruptured and unruptured AVMs and the odd ratios related to the AVMs bleeding risk.

|                      | All patients (n=639) | Ruptured AVMs (n=274) | Unruptured AVMs (n=365) | P    | Odds ratio (95% CI) |
|----------------------|----------------------|------------------------|--------------------------|------|---------------------|
| **Sex (%)**          |                      |                        |                          |      |                     |
| Female               | 318 (50)             | 126 (46)               | 192 (53)                 | 0.098* | 0.767 (0.560-1.050) |
| Male                 | 321 (50)             | 148 (54)               | 173 (47)                 |      |                     |
| **Age, years, mean (range) Vm (%)** | 32.9 (5-82)         | 30.2 (6-68)            | 34.5 (5-82)              | 0.0001** | NA                     |
| < 90 cm/s            | 262 (41)             | 189 (69)               | 73 (20)                  | 0.0001* | 0.112 (0.78)          |
| > 90 cm/s            | 377 (59)             | 85 (31)                | 292 (80)                 |      |                     |
| **Nidus size (%)**   |                      |                        |                          |      |                     |
| < 3 cm               | 433 (70)             | 233 (85)               | 200 (55)                 | 0.0001* | 0.213 (0.144-0.315)   |
| > 3 cm               | 206 (30)             | 41 (15)                | 165 (45)                 |      |                     |
| **Venous drainage Type (%)** |              |                        |                          |      |                     |
| 1A                   | 246 (38.5)           | 81 (29.5)              | 165 (45)                 | 0.0001* | 0.509 (0.365-0.709)   |
| 1B                   | 94 (14.7)            | 24 (9)                 | 70 (19)                  | 0.0001* | 0.405 (0.247-0.663)   |
| 1C                   | 144 (22.5)           | 111 (40.5)             | 33 (9.4)                 | 0.0001** | 6.851 (4.450-10.547)  |
| 2A                   | 72 (11.3)            | 18 (6.5)               | 54 (15)                  | 0.0001* | 0.509 (0.365-0.709)   |
| 2B                   | 63 (9.9)             | 29 (10.5)              | 34 (9.2)                 | 0.0001* | 0.509 (0.365-0.709)   |
| 3A                   | 10 (1.6)             | 3 (1.1)                | 7 (1.9)                  | 0.0001* | 0.509 (0.365-0.709)   |
| 3B                   | 10 (1.6)             | 8 (2.9)                | 2 (0.5)                  | 0.0001* | 0.509 (0.365-0.709)   |
| **Score in our classification (%)** |              |                        |                          |      |                     |
| 1 Points             | 143 (22.4)           | 15 (5)                 | 128 (35.6)               | 0.0001* | 0.107 (0.061-0.188)   |
| 2 Points             | 193 (30.2)           | 39 (14)                | 154 (42)                 | 0.0001* | 0.227 (0.153-0.338)   |
| 3 Points             | 200 (31.3)           | 129 (47)               | 74 (20)                  | 0.0001* | 0.227 (0.153-0.338)   |
| 4 Points             | 103 (16.1)           | 94 (34)                | 9 (2.4)                  | 0.0001* | 0.227 (0.153-0.338)   |
| **SM score**         |                      |                        |                          |      |                     |
| I                    | 150 (23.5)           | 84 (30.6%)             | 66 (18%)                 | 0.0001* | 0.499 (0.345-0.723)   |
| II                   | 237 (37.1)           | 105 (38.3%)            | 132 (36.1%)              | 0.0001* | 0.912 (0.660-1.261)   |
| III                  | 187 (29.3)           | 71 (26%)               | 116 (32%)                | 0.0001* | 1.332 (0.940-1.888)   |
| IV                   | 56 (8.8)             | 14 (5.1%)              | 42 (11.5%)               | 0.0001* | 2.415 (1.291-4.518)   |
| V                    | 9 (1.4)              | 0 (0%)                 | 9 (2.4%)                 | 0.0001* | 0.912 (0.660-1.261)   |

AVMs: Arteriovenous malformations, SM: Spetzler and Martin (SM) classification, CI: Confidence interval. *Chi-square, **Mann-Whitney U test

Figure 6: Grade 2. Lateral cerebral angiogram (A-C) shows Spetzler Martin grade-I AVM, 3 cm in diameter, superficial venous anterograde drainage in TCD presents Mv > 90 cm/sec. Grade 2 in the proposed classification.
aforementioned classifications can accurately determine the risk of bleeding, and patients with low risk cannot be differentiated from patients with high risk.

Our classification based on scores of 1–4 shows an association between risk of rupture in patients with cerebral AVMs and anatomic and hemodynamic variables, thus it is useful in assessing the odds of rupture in AVM; it is easy to use and for the classification we employed very common diagnostic tests that are available in multiple medical centres around the world. In our opinion, all AVMs should be considered different and unique entities, since each of them may have characteristics that confer an individualised rupture risk thereupon. Our scale may help to establish a hierarchy for every AVM based on angiographic and hemodynamic variables, thus assessing a specific and exclusive bleeding risk and allowing for a more accurate determination of the optimal treatment.

The patients at low risk for rupture in our classification arrived at hospital with headache, seizures, or steal phenomenon symptoms. If these subsets of patients are partially embolised, a low-risk lesion can transform into a high-risk lesion and the patients who arrived by headache end up with cerebral hemorrhage. This phenomenon may occur even in near-totally embolised AVMs.[1,18,31,14]

With regard to venous drainage, it is well-known that single deep venous drainage is strongly correlated with brain hemorrhage; however, deep venous drainage associated with superficial venous drainage reduces rupture risk.[19,20]

Some multi-centre studies claim that patients with cerebral AVMs have a better prognosis when treated with pharmacological therapy, since endovascular and surgical procedures increase morbidity; nevertheless these are based on the SM classification, which we found is not predictive of rupture risk,[1,18,21-23] while accounting for its variability to a lesser extent than the proposed classification as indicated by our logistic regression analysis. Management of brain AVMs should not be based on anatomical factors alone, since hemodynamic variables may give a broader view of their behaviour and improve the evaluation of the risk of hemorrhage in each lesion. It is also important to note that we cannot generalise rupture risk specifically in these kinds of shunts. Every shunt, malformation nidus and patient are different from each other[19,20] and this is a well-known limitation of each scale published.

In our study, we observed that a low percentage of patients (19% with a history of hemorrhage and 28%...
without a history of hemorrhage) exhibit upstream or reverse flow venous drainage. This type of venous drainage is almost always associated with fistulous shunts (low resistance and elevated mean velocity lesions with high turbulence and venous hypertension) and it has a high risk of rupture when it is purely superficial, since the flow and pressure in superficial and deep venous drainage have a better means of escape and dispersion. However, we did not analyze this variable in greater detail.

The limitations of our study are those that are common to retrospective studies, the use of selected anatomic and hemodynamic variables of the AVMs, the reproducibility, and consistency of TCD measurements. Notwithstanding the fact that our phenomenological regression modeling approach provided insight into the significance of the proposed variables in explaining rupture risk in patients with AVM, the use of predictive modeling will be necessary in a future study to quantify predictability of the chosen phenomenological variables.

CONCLUSIONS

The present classification is useful and easy to use, and it may allow us to individualise each AVM and assess the risk of rupture of a cerebral AVM based on a model of categorisation.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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