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*Prognostic factors and their impact concerning the therapeutic
algorithm in brain arteriovenous malformations*

SUMMARY OF THE DOCTORAL THESIS

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Introduction

Arteriovenous malformations (AVMs) are complex vascular shunts formed by feeding arteries that converge into an abnormal nidus of blood vessels, comprising arteries and veins, through which blood flows under pressure without the interposition of a capillary bed. This pathology predominantly affects young patients, and its natural progression can significantly impact their quality of life, posing a potential life-threatening risk.

This doctoral thesis aims to evaluate the prognostic factors in the treatment of arteriovenous malformations, with particular emphasis on surgical management. Given that treatment indications and patient prognosis vary depending on the hemorrhagic status of the lesion, another important objective is to identify clinical and morphological characteristics that increase the risk of intracerebral hemorrhage secondary to AVM rupture. A clinical parameter less explored in the literature is the patient's neurological status at the time of diagnosis, which may influence prognosis and, if proven significant, could alter the therapeutic algorithm, especially for unruptured AVMs.

The thesis also proposes a survival study with time-dependent analyses to determine risk factors for overall mortality, with the aim of providing a comprehensive, long-term perspective on this pathology. Furthermore, considering that patients present different profiles based on age, the study will assess the natural history of arteriovenous malformations to identify factors associated with hemorrhagic presentation at young ages.

I. Scientific background

1. Clinical and imaging characteristics of brain AVMs

1.1. Epidemiology

The prevalence of arteriovenous malformations has become easier to assess with advancements in imaging techniques and the widespread availability of MRI devices. It is now estimated at approximately 50 cases per 100,000, based on large-scale studies conducted in apparently healthy populations [1, 2].

1.2. Clinical manifestations

Intracerebral hemorrhage is the most common clinical manifestation of arteriovenous malformations. A meta-analysis reports an overall annual bleeding rate of 3%, with a rate of 2.2% for unruptured lesions and 4.5% for previously ruptured malformations [3]. The overall

mortality rate among these patients is 0.7-2.9% per year [4, 5], while 5-25% of hemorrhages associated with these malformations may be fatal [3, 6-9]. Several factors associated with hemorrhagic presentation have been cited, including previous hemorrhage, younger age, infratentorial or deep location, exclusive deep venous drainage, and larger size [10].

Seizures are another common clinical manifestation of arteriovenous malformations, particularly when located in the frontal and temporal lobes. The risk of seizure occurrence increases with the size of the malformation [11-15]. Large, superficially located, unruptured malformations are frequently associated with seizures [16].

1.3. Imaging characteristics

Arteriovenous malformations require detailed morphological characterization, to determine the location and number of feeding arteries, the draining veins, the size and configuration of the nidus, and the presence of any associated arterial or venous aneurysms [1]. Digital subtraction angiography (DSA) remains the gold standard investigation for precise imaging diagnosis. MRA and CTA can also be employed when DSA is not feasible. Cerebral CT or MRI can detect the nidus, serpiginous vascular structures, calcifications, and flow voids, but they do not provide precise details of the involved vascular elements.

1.4. Particularities related to age and location

Arteriovenous malformations diagnosed in pediatric patients exhibit several distinct characteristics. They are the most common cause of non-traumatic intracerebral hemorrhage, with an annual rupture risk ranging from 2% to 11% [17-20]. Time-dependent analyses have identified supratentorial location, deep venous drainage, and deep location as risk factors associated with hemorrhagic presentation at a young age, whereas nidus and flow-related aneurysms have been linked to malformation rupture in adults [21].

Infratentorial location is another rare and distinct entity for this type of lesion, occurring in 7% to 15% of all arteriovenous malformations [22]. Unlike supratentorial malformations, which may be diagnosed due to epileptic manifestations, infratentorial malformations most commonly present with hemorrhage. Studies report a bleeding rate of 16% for these lesions, with a mortality rate of approximately 66.7% [23-25].

2. Treatment and prognostic factors in brain AVMs

Therapeutic options in vascular neurosurgery have evolved over time, now offering solutions for a wide range of vascular malformations. Treatment options for arteriovenous

malformations include surgical intervention, endovascular therapy, stereotactic radiosurgery, and multimodal treatment, which combines various approaches from the aforementioned methods. Surgical intervention is the ideal therapeutic option, as it eliminates the arteriovenous malformation and, consequently, the risk of hemorrhage, leading to patient recovery. When surgery is not feasible, or in cases of small, unruptured lesions, alternative therapeutic options such as stereotactic radiosurgery or endovascular embolization may be considered.

The main classification used in neurosurgical practice to stratify surgical risks in the treatment of arteriovenous malformations are the Spetzler-Martin classification and the Supplementary Spetzler-Martin classification. Lower grades, SM I and SM II, are associated with low operative risks, while higher grades, SM IV and V, are linked to very high operative risks and typically require multimodal treatment [26]. The Supplementary Spetzler-Martin classification adds three new parameters to the original classification (history of hemorrhage, diffuse or compact nature of the nidus, and patient age), with an operability threshold established at a score of < 7 [27].

II. Personal contributions

3. Working hypothesis and objectives

This study aims to identify prognostic factors in the surgical treatment of arteriovenous malformations (AVMs) and to investigate specific subgroups of this pathology to refine the therapeutic algorithm. Additionally, the natural history of AVMs may influence patient prognosis, and a thorough understanding of this process could significantly contribute to reducing morbidity and mortality.

The study objectives are as follows:

1. Conduct a retrospective analysis of a cohort of consecutive AVMs treated with various therapeutic approaches.
2. Identify predisposing factors for hemorrhage in two distinct categories: infratentorial and supratentorial AVMs.
3. Determine clinical and angiographic characteristics that increase the risk of epileptic manifestations.
4. Evaluate immediate and long-term clinical outcomes in AVM treatment, and establish prognostic factors associated with surgical intervention.

5. Assess patient survival and identify risk factors for long-term mortality.

4. **General Research Methodology**

The thesis encompasses three retrospective, single-center, observational studies. The database included comprehensive demographic, clinical, and angiographic characteristics, along with treatment data, post-procedural complications, and patient follow-up information. Statistical analysis and graphical illustrations were performed using IBM SPSS Statistics for Windows, version 29, and GraphPad Prism, version 10.2.2, for Windows. Statistical significance was defined as $p < 0.05$. The study received approval from the Ethics Committee of the "Bagdasar-Arseni" Clinical Emergency Hospital.

5. **Clinical outcomes of posterior fossa arteriovenous malformations: a single center experience**

5.1. **Introduction**

Infratentorial arteriovenous malformations pose major risks for the patient, especially due to the severe impact of any hemorrhage in this compartment. The mortality rate of posterior fossa AVMs was 10-30% [28], or even up to 50% in some publications [29]. The main goals in treating these lesions are preserving neurologic integrity and eliminating the hemorrhage risk and its severe clinical consequences. Being a rare pathology, existing literature on infratentorial AVMs predominantly comprises descriptive studies. The aim of this study was to analyze the clinical and imaging features in a retrospective cohort of posterior cranial fossa AVMs, to identify the factors that influence the prognosis of these patients.

5.2. **Patients and methods**

The study is a retrospective, observational, single-center, observational study that included patients hospitalized at the "Bagdasar-Arseni" Emergency Clinical Hospital between January 1997 and December 2021. Patients with the diagnosis of infratentorial AVM, as determined by DSA, CTA, MRA and/or confirmed by histopathologic findings, were included in the study. Exclusion criteria were represented by AVMs located in both compartments (supra- and infratentorial), patients treated before at other institutions, or who presented in an extremely severe clinical and neurological condition who did not tolerate further angiographic investigations. Data management and methods regarding statistical analysis were described in chapter no. 4 - "General research methodology". Fisher's exact

test was used for univariate analysis of categorical variables, and the Baptista-Pike and Woolf methods were used for odds ratios and confidence intervals, as appropriate. Logistic regression was used for multivariate analysis, while the Kaplan-Meier analysis was used to assess the role of factors associated with hemorrhagic presentation in time-dependent analysis.

5.3 Results

The initial cohort included 53 patients, and following selection according to exclusion criteria, the study group comprised 48 patients. A favorable mRS score (mRS < 3) at presentation was observed in 33 patients (69%). Thirty-four patients (71%) presented with ruptured AVM. Of these, 19 cases (40%) also presented with intraventricular hemorrhage. Thirty-three patients (69%) underwent microsurgical resection, seven patients (15%) were treated conservatively, six patients (12%) underwent stereotactic radiosurgery, and two patients (4%) were treated by endovascular embolization. Multimodal treatment was necessary in five cases.

Predisposing factors for bleeding presentation in infratentorial AVMs

Patients aged ≤ 30 years presented more often with ruptured AVMs (OR 5.23; 95%CI 1.42-17.19; $p = 0.024$), and this association retained its statistical significance in multivariate analysis (OR 4.81; 95%CI 1.07-21.53; $p = 0.040$). Male sex was also statistically associated with hemorrhagic presentation in multivariate analysis (OR 5.21; 95%CI 1.01-26.77; $p = 0.048$). According to the Log-Rank test, as part of the Kaplan-Meier analysis, patients harboring infratentorial AVMs with associated aneurysms were diagnosed with hemorrhagic presentation at older ages compared to the rest of the study group. The median age of hemorrhagic presentation in patients with aneurysms was 51 years while for the group without associated arterial aneurysms the median age was 21 years (HR 0.32; 95%CI 0.14-0.71; $p = 0.016$).

Clinical outcomes in treating infratentorial AVMs

We tested the impact of several clinical and imaging features in relation to the patient prognosis, using the mRS score at discharge. Deep venous drainage ($p = 0.021$), increased number of feeding arteries (more than 2 feeding arteries) ($p = 0.002$), ruptured AVMs ($p = 0.039$), intraventricular hemorrhage ($p < 0.001$) and involvement of eloquent areas ($p = 0.034$) were statistically associated in univariate analysis with an unfavorable outcome at discharge, defined by an mRS score > 2 .

Prognostic factors associated with surgical treatment

Thirty-three patients received microsurgical resection of the malformation. Univariate analysis detected several factors associated with an unfavorable postoperative outcome (mRS > 2): altered neurologic status on admission mRS > 2 (OR 110.5; 95%CI 9.12-1208; $p < 0.0001$), more than two feeding arteries (OR 12.1; 95%CI 2.09-63.79; $p = 0.008$), intraventricular hemorrhage (OR 16.8; 95%CI 2.87-86.02; $p = 0.001$), bleeding history (OR 11.7; 95%CI 1.55-136.6; $p = 0.021$). Of these, only altered neurologic status on admission was found to be an independent risk factor for an unfavorable postoperative outcome in multivariate analysis (OR 96.14; 95%CI 5.15-1793.9; $p = 0.002$).

5.4. Discussion

Factors associated with hemorrhagic presentation

Patient age proved to be a predictive factor for hemorrhagic presentation, with younger patients being almost five times more at risk to be diagnosed with ruptured AVMs, compared to other age groups. Similar results were reported by Tong et al. who identified young age as an independent factor for hemorrhagic presentation in infratentorial AVMs [30], but there are also studies that attributed this increased risk to age over 60 years [31, 32].

Patients harboring AVMs with associated aneurysms were diagnosed with hemorrhage later in life, compared to the rest of the cohort, the median age of hemorrhagic presentation being 51 years in the former category and 21 years in the latter. A possible explanation for this association was published by Garzelli et al, who identified a similar correlation. They mention that arterial aneurysms develop later in life, due to hemodynamic consequences on the arterial vessels and thus are associated with older ages of hemorrhagic presentation [21].

Prognostic factors in the treatment of infratentorial AVMs

The hemorrhagic status of the lesion significantly influenced the patient's condition at discharge, with unruptured AVMs having a favorable outcome in 93% of cases, whereas ruptured AVMs were discharged in good condition in only 62% of cases, the association being also published in several studies in the literature [33-35]. Deep venous drainage was another significant prognostic factor in this cohort, with many explanations for its crucial role. Deep venous drainage also involves deep arterial feeders, which makes surgical resection more difficult, and coagulation of deep draining veins and reorganization of venous flow in those territories may have side effects in eloquent infratentorial areas [36]. The latest classification of cerebellar AVMs includes deep drainage, along with the patient's age and neurologic status on admission, as determinants of patient prognosis [37].

Treatment considerations of infratentorial AVMs

The only factor that proved to independently influence the postoperative outcome, in multivariate analysis, was the initial neurologic status of the patient. The correlation has also been published in other studies related to the treatment of infratentorial AVMs [24, 38, 39], and Yang et al. found a significant association between the hemorrhagic presentation and the patient's neurologic status at diagnosis [39]. All this information orients the therapeutic attitude towards interventional treatment of infratentorial AVMs shortly after diagnosis, before a possible rupture or a new hemorrhagic episode, with the aim of maintaining the patient's functional integrity [32, 38, 40].

5.5 Conclusions

Infratentorial AVMs are challenging vascular lesions due to their location and frequent association with hemorrhagic presentation. Unruptured AVMs have a better clinical course compared to ruptured ones, and the risk of hemorrhage is significantly higher in patients younger than 30 years old. Neurologic status on admission was the only independent prognostic factor for surgically treated patients. Treatment indications for ruptured AVMs are quite clear in the literature. In terms of addressing unruptured malformations, after careful selection, surgical treatment can yield good functional outcomes while also eliminating the risk of future hemorrhage.

6. Surgical outcomes and risk factors for overall mortality in brain arteriovenous malformations patients. A retrospective analysis

6.1. Introduction

This study aims to identify factors that influence short-term clinical outcomes and long-term mortality. Constant evaluation of prognostic factors in the treatment of AVMs allows improving the therapeutic algorithm and its personalization according to the particularities of each case. Kato et al. published a series of recommendations in the field of vascular neurosurgery, in which they emphasized the need to include the patient's neurologic status on admission in a new classification, along with other important characteristics [41]. In the present study, we evaluated the influence of this clinical characteristic regarding the patient's outcomes and its significance in relation to other decisive prognostic factors. We also evaluated the mortality rate for several categories of patients in the cohort over a 12-year follow-up period, mainly targeting patients who received interventional treatment

(surgical treatment, endovascular embolization, stereotactic radiosurgery), compared to patients treated conservatively.

6.2. Patients and methods

The study was observational, retrospective and single-center and included 248 consecutive patients hospitalized at the "Bagdasar-Arseni" Emergency Hospital between January 2012 and December 2022. Exclusion criteria included patients in deep coma, whose clinical condition did not allow further investigations, arteriovenous fistulas, complex intra/extracranial AVMs, and patients with a histopathologic confirmation of AVM, but who only performed a CT scan before surgery (ruptured AVM operated in emergency). The final study cohort included 191 patients. Demographic, clinical and morphologic data were recorded for each case. The vital status of the patients was obtained from the Population Registry Service on January 12th, 2024.

6.3 Results

Of the 191 cases (98 male patients and 93 female patients), 94 were ruptured AVMs (49.2%). The treatment of choice was microsurgical resection, which was performed in 79 patients (41.4%), endovascular embolization was performed in 21 cases (11%), and stereotactic radiosurgery was the treatment of choice for 36 patients (18.8%). The conservatively treated group comprised 55 patients, while 14 patients (7.32%) required multimodal treatment.

Surgical treatment and degree of resection

Complete resection of the AVM was performed in 68 cases (86.1%). Incomplete resection was statistically associated with Spetzler-Ponce (SP) grade C AVMs, compared with SP grade A or B lesions (OR 6.1; 95%CI 1.5-23.6; $p = 0.005$). Furthermore, deep venous drainage similarly increased the risk of incomplete resection (OR 5.5; 95%CI 1.1-27.6; $p = 0.047$).

Prognostic factors associated with surgical treatment

The subgroup of surgically treated patients had 79 cases, 43 of whom were hospitalized in good clinical and neurologic status ($mRS \leq 2$). At discharge, 55 cases (69.9%) had a mRS score ≤ 2 . The mRS value improved in 65 cases (82.3%), seven patients were discharged in similar condition as they were admitted, and in seven cases their condition worsened.

Multivariate logistic regression was used to highlight independent prognostic factors in relation to surgical treatment, which detected the following covariates as statistically significant: female sex (OR 3.32; 95%CI 1.03-10.7, $p = 0.044$), altered neurological status on admission - $mRS > 2$ (OR 4.68; 95%CI 1.32-16.57, $p = 0.017$) and involvement of

eloquent area (OR 3.79; 95%CI 1.07-13.4, $p = 0.038$). The area of the ROC curve of this regression model with the three prognostic factors was 0.824.

Postoperative neurologic worsening was associated in univariate analysis with increasing grade on the Supplementary SM (SuppSM) scale. Lesions with a SuppSM grade greater than six demonstrated significantly higher risks of neurologic deterioration compared to the rest of the cohort (OR 7.3; 95%CI 1.4-37; $p = 0.023$). Moreover, multiple venous drainage had a similar influence on the risk of neurologic worsening (OR 2.4; 95%CI 1.2-4.7; $p = 0.009$).

Prognostic factors in the entire cohort

To gain an overview of the entire study group, prognostic factors associated with AVM treatment in the entire study cohort were analyzed. According to multivariate logistic regression, involvement of eloquent areas (3.01; 95%CI 1.14-7.94; $p = 0.025$), female sex (OR 4.4; 95%CI 1.37-14.1; $p = 0.013$) and altered neurologic status on admission (OR 20.38; 95%CI 6.53-63.55; $p < 0.001$) were independent risk factors for an unfavorable outcome at discharge. The area of the ROC curve of the regression model with the three significant covariates was 0.894.

Survival analysis and risk factors for overall mortality

By January 12th, 2024, of the total 191 patients, 20 were deceased (10.47%), out of which 10 patients died within the first six months (six patients died while being hospitalized). Ten deaths were from the conservatively managed group of patients. The surgically treated group had seven deaths, three of these within the first six months.

The Kaplan-Meier analysis of the surgical group revealed the following factors associated with increased overall mortality: nidus size (< 3 cm versus 3-6 cm, $p = 0.039$; < 3 cm versus > 6 cm, $p = 0.007$), involvement of eloquent areas ($p = 0.021$), age > 40 years ($p = 0.028$), high grade on the SP scale (SP C versus SP A and SP B, $p = 0.009$); high grade on the SuppSM scale (SuppSM > 6 versus SuppSM < 4 , $p = 0.008$; SuppSM > 6 versus SuppSM 5-6, $p = 0.039$).

Analysis of the entire cohort revealed the following factors associated with high overall mortality: eloquent areas involvement ($p < 0.001$), age (< 20 years versus > 40 years, $p = 0.01$; 20-40 years versus > 40 years, $p = 0.002$); mRS on admission > 2 ($p = 0.005$); comorbidities ($p = 0.006$); high grade on the SP scale (SP B versus SP A, $p = 0.048$; SP C versus SP A, $p < 0.001$); high grade on the SuppSM scale (SuppSM > 6 versus SuppSM < 4 , $p = 0.001$; SuppSM > 6 versus SuppSM 5-6, $p = 0.012$); conservative versus interventional treatment ($p = 0.020$).

Cox proportional hazards regression performed on the entire study group identified the following independent risk factors for increased overall mortality: conservative treatment (HR 2.7; 95%CI 1.1-6.6; $p = 0.030$), mRS > 2 on admission (HR 4.5; 95%CI 1.8-11; $p = 0.001$) and age over 40 years (HR 5.5; 95%CI 2-15.4; $p = 0.001$). The covariates also maintained their significance when testing the subgroup of patients with SM I-III AVMs, which accounted for 145 cases and 10 deaths.

The study group also included 59 ARUBA eligible patients, with two deaths in this subgroup, belonging to conservatively treated patients. The Kaplan-Meier analysis demonstrated some differences between the interventional and conservative treatment groups, without reaching statistical significance ($p = 0.057$).

6.4. Discussion

Neurologic status on admission

Altered neurologic status on admission, a prognostic factor in the study surgical cohort, has been cited in several publications to have a negative impact on the surgical treatment of AVMs [33, 38, 39, 42-44]. Survival analysis also identified the impact of this clinical characteristic on overall mortality. Taking these aspects into account, the decision-making process in determining the optimal therapeutic strategy in unruptured AVMs requires consideration of both the risk/benefit ratio of an elective intervention, but also the risks of a conservative approach followed by surgery in case of intracerebral hemorrhage. Altered neurologic status associated with a hemorrhagic event may affect both postoperative prognosis and long-term survival.

The impact of patient's age

Age over 40 years, cited in several publications as a negative prognostic factor in both short and long-term prognosis [45] and included in the well-known SuppSM classification [46], negatively influenced AVM patient survival in the present study. Given that the risk of hemorrhage in untreated lesions is permanent and may increase with age [47], it is important to counsel the patient regarding the risks of ageing with an untreated vascular pathology that may require therapeutic intervention in the future.

Conservative treatment compared to other therapeutic approaches

Patients treated by interventional methods (surgical treatment, SRS, endovascular treatment) had significantly better survival compared to those treated conservatively. Because the group of patients treated conservatively showed higher grades on the SM scale, we analyzed also the group of SM I-III AVMs, and the association between conservative

treatment and a higher overall mortality rate maintained statistical significance in Cox regression. The results of the survival analysis confirm that, after judicious case selection, arteriovenous malformations, and especially grade I-III, can and should be treated [34, 41, 48, 49].

6.5. Conclusions

The study identified female sex, altered neurological status on admission and involvement of eloquent areas as negative prognostic factors for short-term clinical outcomes. Patients receiving interventional treatment had superior survival rates compared to those managed conservatively. Treating patients with brain AVMs whenever the risk/benefit ratio is in the patient's favor may increase long-term survival, and the therapeutic decision should also consider that the patient's age as well as the neurologic status on admission influence overall long-term mortality.

7. Natural history and predictors for hemorrhage in supratentorial brain arteriovenous malformations

7.1. Introduction

Although infratentorial AVMs are well-known for their very high percentage of hemorrhagic presentations, supratentorial lesions as well are diagnosed ruptured in more than 50% of cases in some series [50]. Epileptic seizures are the second most common clinical manifestation of AVMs developed in this compartment. This study aims to evaluate the natural course of supratentorial AVMs and to highlight some factors associated with the hemorrhagic presentation as well as epileptic manifestations.

Due to the rare nature of this pathology, there are few extensive, multi-centric follow-up studies with very long follow-up periods, that can offer a realistic assessment of the natural history of AVMs. For this reason, we decided to use the “birth to diagnosis” timeline to assess the hemorrhage rate and risk factors associated with hemorrhagic presentation of AVMs. According to the comparison by Kim et al., this method offers similar results to the conventional one, that uses the “diagnosis to hemorrhage” timeline [51].

7.2. Patients and methods

The study is an observational, single-center, retrospective one. Over a period of 11 years (2012-2022), 198 patients with supratentorial AVMs were admitted to "Bagdasar-Arseni" Clinical Emergency Hospital. The exclusion criteria were patients without angiographic investigations, AVMs located in both compartments, and AVMs associated

with AVFs. The final study cohort after excluding these cases had 169 patients. Data collection and statistical analysis methods were presented in Chapter 4 – “General research methodology”. The hemorrhage rate was calculated using the formula: (number of patients diagnosed with ruptured AVM) / (total number of patient-years of follow-up) x 100 [51].

7.3. Results

Of the 169 patients, 86 (50.9%) were male. The proportion of pediatric patients was 16%, and 81.3% of them presented with ruptured AVMs. Seventy-eight patients were diagnosed with ruptured AVMs, while 77 patients (45.6%) presented for epileptic seizures.

Hemorrhagic presentation

The number of patient-years of the follow-up according to the method using the “birth to diagnosis” timeline summed 6054. The bleeding rate under these conditions was 1.28% / year for lesions with no previous history of hemorrhage.

Factors associated with hemorrhagic presentation

Univariate analysis identified several characteristics associated with hemorrhagic presentation in the study group: deep location (OR 2.7; 95%CI 1.1-5.1; $p = 0.017$), pediatric age (OR 5.2; 95%CI 2-13.7; $p < 0.001$), nidus < 3 cm (OR 2.4; 95%CI 1.3-4.5; $p = 0.005$). We introduced in the multivariate logistic regression model all variables that proved significant in the univariate analysis, and they maintained their significance, being independently associated with hemorrhagic presentation: nidus size < 3 cm (OR 2; 95%CI 1.07-3.9; $p = 0.03$); pediatric age (OR 4.5; 95%CI 1.6-12.2; $p = 0.003$); deep localization (OR 2.3; 95%CI 1.06-5.1; $p = 0.035$).

Kaplan-Meier analysis using the “birth to diagnosis” timeline

Using this method, we analyzed the impact of several clinical and morphological features regarding the hemorrhagic presentation during the patient's lifetime until diagnosis. Patient's age served as the time variable, and the event of interest was the hemorrhagic presentation. The aim of the analysis was to assess the likelihood of a supratentorial AVM to be diagnosed unruptured, across the patient's lifetime, depending on several factors.

The Kaplan-Meier analysis detected the following factors associated with a hemorrhagic presentation at a young age: nidus < 3 cm ($p = 0.017$) and exclusively deep venous drainage ($p = 0.058$). Unique venous drainage ($p = 0.058$), deep located nidus ($p = 0.052$) and unique feeding artery ($p = 0.057$) demonstrated some differences, but without reaching statistical significance.

Cox regression

Exclusively deep venous drainage, small nidus size and deep located nidus were included in the Cox multivariate regression analysis. Exclusively deep venous drainage had the greatest impact, increasing the risk of hemorrhage by more than 2-fold (HR 2.2; 95%CI 1.2-4; $p = 0.009$). Patients with small size AVMs also had an increased independent risk of bleeding compared to the rest of the cohort (HR 1.8; 95%CI 1.09-2; $p = 0.022$). Deep located nidus did not reach statistical significance (HR 1.3; 95%CI 0.73-2.31; $p = 0.361$).

Shifting the “birth to diagnosis” curve by 10 years

According to the article by Kim et al., the two methods "birth to diagnosis" and "diagnosis to hemorrhage" are most similar when the "birth to diagnosis" curve is shifted by 10 years [51]. We applied this method, and the new group of patients had 160 cases. The Kaplan-Meier analysis revealed the following factors associated with hemorrhagic presentation at a young age: nidus size < 3 cm ($p = 0.027$), exclusively deep venous drainage ($p = 0.015$) and unique feeding artery ($p = 0.037$).

Epileptic seizures in supratentorial AVMs

Epileptic seizures in the study group were associated in univariate analysis with unruptured AVMs (OR 3.1; 95%CI 1.6-5.9; $p < 0.001$), nidus size > 6 cm (OR 3.2; 95%CI 1.07-9.5; $p = 0.029$) and superficial venous drainage (OR 2.3; 95%CI 1.2-4.3; $p = 0.008$). Superficially (cortical) located nidus demonstrated borderline results (OR 2.1; 95%CI 0.99-4.5; $p = 0.049$). The variables were then entered in multivariate analysis, that revealed the following factors independently associated with epileptic seizures: unruptured AVM (OR 3.1; 95%CI 1.6-6.2; $p = 0.001$), superficial venous drainage (OR 2.7; 95%CI 1.3-5.7; $p = 0.007$) and nidus size > 6 cm (OR 4; 95%CI 1.2-13.5; $p = 0.025$).

Epileptic seizures in the unruptured AVM group

The same characteristics tested in the entire cohort were also used to assess factors associated with epileptic seizures in the unruptured AVMs subgroup. There were 91 cases with unruptured AVMs, 53 of whom had epileptic seizures on admission. Superficial venous drainage proved its association in this setting as well (OR 2.9; 95%CI 1.2-6.9; $p = 0.014$). The size of the nidus larger than 6cm did not retain its significance, probably due to the very small number of cases (there were 12 AVMs with nidus > 6 cm and 8 of them presented with epileptic seizures). Frontal/parietal/temporal location was another characteristic statistically associated with this symptom (OR 3; 95%CI 1.2-7.7; $p = 0.015$). Superficial venous drainage and frontal/parietal/temporal localization were included in multivariate analysis, which detected the following associations: unruptured AVMs with frontal/temporal/parietal location are 2.7 times more likely to have epileptic seizures (OR 2.7; 95%CI 1.04-6.9; $p =$

0.040), and superficial venous drainage increases the risk of epileptic seizures by 2.6 times (OR 2.6; 95%CI 1.06-6.3; $p = 0.036$).

7.4 Discussion

Hemorrhagic presentation in supratentorial AVMs

Intracerebral hemorrhage secondary to AVM rupture can significantly alter the patient's neurologic status and prognosis [42], therefore it is important to assess risk factors for hemorrhagic presentation and to adjust therapeutic strategies in unruptured AVMs according to the characteristics of each lesion. In the study cohort, pediatric patients were more frequently diagnosed with ruptured AVMs, as were patients with lesions smaller than 3 cm in size and those deeply located. The more aggressive nature of AVMs in the pediatric population is debatable [32], a possible explanation for the increased percentage of ruptured AVMs in this population segment being the reduced number of investigations that pediatric patients undergo for minor complaints such as headache, or for other pathologies, which could lead to the incidental discovery of an AVM [52].

A similar theory has also been developed about small AVMs, which do not manifest mass effect and are not diagnosed for other symptoms until a hemorrhagic event [10]. There are also authors that have associated small nidus size with increased feeding artery pressure, which may increase the risk of hemorrhage [53]. For this reason, it is necessary to clearly distinguish between factors associated with hemorrhagic presentation and risk factors for possible AVM rupture.

Bleeding rate and risk factors for early hemorrhagic presentation

The hemorrhagic rate calculated in the current study cohort was 1.28%/year, similar to those reported for AVMs in general [10, 51, 54]. It is important to emphasize is that although infratentorial AVMs are associated with a high frequency of hemorrhagic presentations [40], this risk should not be overlooked for supratentorial lesions as well.

Exclusively deep venous drainage, unique feeding artery, and small nidus size were associated in time-dependent analyses with hemorrhagic presentation at a young age. Given these correlations, it is recommended that unruptured supratentorial AVMs with these features receive interventional treatment to prevent a hemorrhagic episode and its potentially severe clinical consequences. Although the use of this method is not as precise as the conventional one, the timeline from birth to diagnosis has been used by other authors as well [55, 56] and has the advantage of using a very long follow-up period.

Epileptic manifestations secondary to supratentorial AVMs

Studying the pathophysiologic mechanisms that lead to epileptic manifestations is very useful in the overall treatment of this pathology but is of particular importance especially in cases diagnosed incidentally, or with minor symptoms such as headache. Epileptic seizures have a major impact on the patient's quality of life, and some authors have estimated a 58% risk of developing epilepsy 5 years after the onset of the first seizure in patients with cerebral AVMs [57].

In the overall study cohort, superficial venous drainage, nidus greater than 6 cm, and unruptured lesions were independently associated with seizure onset. In malformations without a history of hemorrhage, frontal/temporal/parietal location and superficial venous drainage were the two independent risk factors associated with this symptom. Regarding the most frequent location, although there have been various associations published in different studies [58-60], the implication is the same: the lesion that develops closely to the neocortex over a large area increases the risk of seizure occurrence. Given these facts, patients with supratentorial AVMs with a high-risk profile for developing epileptic seizures should be counseled not only regarding the risks and benefits of treatment compared to the conservative approach, but also regarding the impact of epilepsy on the quality of life.

7.5. Conclusions

Intracerebral hemorrhage and epileptic seizures are the most important manifestations of AVMs. Small nidus, pediatric age and deep location were statistically associated with hemorrhagic presentation. In time-dependent analyses using the interval from birth to diagnosis, exclusively deep venous drainage, small nidus size, and unique feeding artery were risk factors for early hemorrhagic presentation.

Supratentorial unruptured AVMs were most often diagnosed for epileptic seizures, and superficial venous drainage and location in the frontal, parietal, or temporal lobes significantly increased the risk of epileptic seizures in this subgroup. We consider important for the therapeutic approach of unruptured AVMs to consider the risk of developing epilepsy in the future, in addition to the permanent risk of intracerebral hemorrhage, to determine the optimal treatment choice for each patient.

8. Conclusions and personal contributions

8.1. Conclusions

Cerebral arteriovenous malformations represent dynamic vascular lesions, with different natural history and prognosis depending on their location. The infratentorial

location was quite rare in our cohort as well, compared to the supratentorial compartment. The first study of the PhD thesis was a detailed analysis of the clinical outcomes in the treatment of infratentorial AVMs, a pathology published in the literature predominantly in purely descriptive studies. The study detected two factors associated with hemorrhagic presentation in multivariate analysis: age younger than 30 years of age and male sex. Several clinical and imaging features correlated with the patient's neurologic status at discharge were detected, but the only independent risk factor for an unfavorable postoperative outcome was found to be the altered neurologic status on admission. Due to the severe consequences of an AVM rupture in the posterior fossa, the treatment of unruptured infratentorial AVMs requires a proactive attitude in order to obliterate the lesion as quickly as possible, to prevent a future bleeding episode, especially in young patients with increased bleeding risk and increased life expectancy.

The second study analyzed a cohort of 191 patients with AVMs treated by several therapeutic alternatives (surgical, endovascular, SRS, conservative). The objectives were to determine prognostic factors associated with surgical treatment and to evaluate factors that increase overall long-term mortality in the entire cohort. Female sex altered neurologic status on admission, and eloquent areas involvement were found to be negative prognostic factors for postoperative outcomes in the surgical treatment of AVM. The most significant factor was the patient's admission mRS score. Three risk factors for overall long-term mortality were identified from the survival analysis: age > 40 years, admission mRS score > 2 and conservative treatment (as opposed to interventional treatment). Patients treated conservatively had a 2.7-fold increased risk of death compared to the rest of the study cohort, and the association maintained statistical significance when tested in the subgroup of patients with SM I-III AVMs.

The third study analyzed the natural history of supratentorial AVMs to highlight factors associated with hemorrhagic presentation and those associated with epileptic seizures. Small nidus size, pediatric age and deep location of the malformation were independently associated with hemorrhagic presentation. Furthermore, small nidus size, deep venous drainage, and unique feeding artery were risk factors for early hemorrhagic presentation. Epileptic seizures secondary to AVMs were frequently diagnosed in unruptured, large or superficially draining lesions. As for the subgroup of unruptured AVMs, epileptic seizures were frequently associated with superficial venous drainage and with frontal, parietal or temporal location. The therapeutic algorithm in unruptured AVMs should consider both the risk factors for hemorrhage and the risk to develop epilepsy. The aim in

these cases is to exclude the lesion and thus decrease the risk of epileptic seizures as well as to eliminate the hemorrhagic risk.

2.2. Personal contributions

In this thesis I outlined several factors associated with various forms of presentation as well as multiple prognostic factors associated with surgical treatment.

1. In sub-chapter 6.3.7. of Study II we conducted a survival study, taking data on patients' vital status from the National Population Register one year after the end of the inclusion period. Various factors associated with overall mortality were highlighted, and the most important association in this chapter was the one between interventional treatment and increased patient survival, both in the overall cohort and in the subgroup of patients with AVMs SM grade I-III.

2. Study II sub-chapter 6.3.5. identified the patient's neurologic status on admission as an independent prognostic factors in the surgical treatment of AVMs and demonstrated its superiority over the hemorrhagic status of the AVM. Neurologic status on admission is an important independent prognostic factor, and the therapeutic algorithm for unruptured AVMs requires assessment of both operative or procedural risks and the potential severe functional consequences of a hemorrhagic event during the follow-up period of a conservatively treated lesion.

3. Study III sub-chapter 7.3.2 evaluated the impact of several clinical and morphologic features on the age of hemorrhagic presentation using the “birth to diagnosis” timeline. Although the method has been used before, Kim et al. demonstrated that the two curves corresponding to the “birth-to-diagnosis” and the “diagnosis-to-hemorrhage” timelines are identical when the “birth-to-diagnosis” interval is shifted by 10 years [51]. We thus performed Kaplan-Meier survival curves for both the "birth to diagnosis" and the “10 years to diagnosis" intervals and thus three risk factors associated with hemorrhagic presentation at young age were detected: small nidus size, exclusively deep venous drainage and unique feeding artery. The use of this method provides a longer time frame than any other follow-up period and may provide valuable information on the long-term behavior of AVMs.

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