Title: Predictors of Cerebral Arteriovenous Malformation Mortality: A Single-center, Five-year Retrospective Study

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Contributor Role	Role Definition	Authors					
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Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.	x		x	x		
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.			x			x
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Funding Acquisition	Acquisition of the financial support for the project leading to this publication.	x					x
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.	x	x		x	x	

Methodology	Development or design of methodology; creation of models		X		X	X	
Project Administration	Management and coordination responsibility for the research activity planning and execution.	X	X				X
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.		X	X			X
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.		X	X			X
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.	X	X				X
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.		X	X			X
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.				X	X	
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).				X	X	
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.	X	X	X	X	X	X

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ABSTRACT.

Background: Arteriovenous Malformations are abnormalities in the intracranial vessels between the arterial and venous systems. They are seen as congenital lesions with a poorly understood pathogenesis, although in adults they could be acquired. The aim of this study was to identify predictors of mortality amongst patients and correlate them to available literature

Methods: An analytical, observational and retrospective study design was performed to review data of patients with cerebral arteriovenous malformations in the University Hospital "Dr. José Eleuterio González" from January 2016 to December 2020. The clinical files of patients affected by arteriovenous malformations reported with the International Classification of Diseases 10th Revision, ICD-10, were reviewed.

Results: 80 patients were included in our study. Most (56.3%) were female and only three were pregnant. In a significant portion of the cases, active intracranial bleeding was found in the patients, the most common symptom was holocranial headache occurring between the hours of 22:00 to 7:00 o´clock. There was consistent distribution of the arteriovenous malformations on the left and on the right side with predominance in the frontal lobe (30%). Total area greater than 9.18cm^3 (p-value 0.010), the presence of more than one symptom (p-value 0.041) and a history of previous cerebral intraparenchymal hemorrhage (p-value 0.014) were the most significant predictors factors.

Conclusion: The results demonstrated an important association between intracranial bleeding and mortality; moreover, children were also considered to be at greater risk of mortality. Ultimately, more prospective studies are needed to determine predictor factors for mortality in patients with arteriovenous malformations.

Key Words: Arteriovenous Fistula, Cerebral Hemorrhage, Intracranial Hemorrhages, Nervous System Malformation. (Source: MeSH-NLM).

INTRODUCTION.

Arteriovenous Malformations (AVMs) are abnormal intracranial vessels between the arterial and venous systems.[1] They consist of an abnormal vascular structure dilatation, forming a nest between the two systems with a lack of capillaries, causing arterial blood to reach the venous system.[2] In turn, the formed nest has its own irrigation system, formed by its own arteries (classically referred to as vasa-vasorum); however, unlike healthy blood vessels, these lack normal innervation - therefore lacking the ability to self-regulate arterial flow within the nest.[3]

Although in adults they are seen as possibly acquired malformations; in infants they are thought to be congenital.[4] They are classified as congenital lesions whose pathogenesis is poorly understood, theorizing their development during embryogenesis of the primordial vascular system between weeks three and twelve, and, therefore, being present at birth.[4]

It is found that the most common clinical presentations of cerebral AVMs in pediatric patients is their sudden rupture; the first signs and symptoms being those associated with intracerebral hemorrhage in 41-79% of cases.[5]

The average age of appearance of AVMs is generally between 20-40 years, without specific gender prevalence. Despite being more common in adults, the probability of a rupture is lower in the adult population, than it is in the pediatric patients, hypothesizing that there could be an association between the hormonal changes of puberty with this association, which is why it is believed that the hormonal changes of pregnancy could also represent a period of increased risk of rupture.[6] However, rupture and consequent hemorrhage is still the most common onset of symptoms.[6] When left untreated, the annual probability of rupture ranges between 2.10-4.12%.[7] We have not come across any epidemiological study to determine the most common onset of AVMs in Mexican pediatrics patients.

Of the total number of patients affected by AVMs, it is found that the pediatric population makes up to 3%, and although rare, AVMs represent the most common cause of spontaneous intraparenchymal hemorrhage in children. Furthermore, the general clinical history of AVMs rupture is not clearly established.[9]

The most important classification within this pathology is the one described by Spetzler and Martin in 1986 and it is used to estimate the best therapeutic approach in patients with cerebral arteriovenous malformation. [10] The Spetzler Martin Grading Scale has a range from I to VI, where grade I represents a small, superficial malformation in a non-eloquent portion of the cortex, whereas grade V represents a large, deep malformation in an eloquent portion of the cortex, and grade VI is an inoperable AVM.

For the diagnosis and visualization of AVMs, angiography is considered the gold standard because it allows the physician the diagnostic visualization and to plan the treatment. [11,12] In any case, the initial visualization is intended to be non-invasive, which is why Computed Tomography (CT), or Magnetic Resonance Imaging (MRI) is often used, especially in patients with diffuse or non-specific symptoms such as seizures or headaches. A CT scan is considered superior to MRI for observing vasculature, however, an MRI is a better choice for visualizing adjacent structures and planning of the treatments.[13,14,15]

The therapeutic management includes modalities of surgical resection, endovascular embolization, and stereotactic surgery (particularly in those with a nest smaller than 3 cm in its largest diameter). Currently, attempts have been made at developing a non-invasive medical or expectant medical treatment, with little to no recovery period, for patients with unruptured AVM. [16,17,18]

Current literature on the subject is not specific for the Mexican community, or even Latinos in general, so it cannot be generalized for the adult or pediatric population of Mexico. Moreover, although there are some information available, these are of suboptimal quality.[6,14] For this reason, we decided to review the experience of a single, third-level center, in treating AVMs over the last five years with the objective of generating AVMs epidemiological datasets and mortality-associated markers in among the Latin-American population.

PATIENTS AND METHODS.

Study design

An analytical, observational, retrospective study design was conducted.

Participant

We reviewed available data of patients who were hospitalized at the UANL University Hospital from January 2016 to December 2020 for cerebral AVMs, regardless of whether their malformation had ruptured. Through the collection of data provided by the statistics department of our institution, the clinical files and CT images of patients affected by AVMs were reviewed. In order to obtain all existing patient data from our institution, patient files were identified using the following ICD-10 codes: Q27, Q28, I60, I62 and I69 – with our main focus on Q28. The size of the sample was made by convenience, since the studied sample was the total population in the last 5 years. We included all patients from any department or service within our hospital who were diagnosed with a cerebral AVM, ruptured or not. We excluded patients who were shown to not have a cerebral AVM and whose pathology-oriented medical review had demonstrated a differential diagnosis such as cavernous angioma or capillary telangiectasias, among others.

Variables

Clinical and demographic data such as sex, age, time of evolution, type of treatment, imaging findings, previously known data of predictors factors, and comorbidities, were obtained. In addition, data such as: mortality, subsequent or previous rupture at the time of diagnosis, days of hospitalization, and time and place of rupture was extracted from patient registries.

Procedure

A review of the clinical records was carried out. We included patient data from within the last five years because that is the maximum time a patient's file is kept after their hospitalization. Finally, an Excel database was created in order to extract relevant data.

Statistical Analysis

The population studied was divided into those with a rupture and those without a rupture of an AVM at the moment of arrival in our institution. For the analysis, IBM SPSS Software 23.0 version[19], RStudio version 4.0.2 (2020-06-22), and ggplot2 package were used. To compare the data between the groups, the T-student test and the Chi-square test were used depending on the type of variables, and for correlations we used Pearson's correlation coefficient. A $p < 0.05$ was considered statistically significant. Variables that resulted in statistically significance were included in a logistic regression model.

RESULTS.

Sociodemographic Characteristics

Using the ICD-10 codes, a total of 486 files were obtained. Out of these, we included 80 patient files for subsequent analysis. The average age of our patients was 26.9 ± 17.5 and just over half of the population was female N=45 (56.3%), out of which three were pregnant at the time of consultation.

Clinical Presentation

We found that patients have most commonly presented with more than one symptom, holocranial headache being the most common in 34(23.9%) patients, followed by a generalized tonic-clonic seizure in 29(20.4%) patients, and lastly with a loss of consciousness in 24 (16.9%) patients. Only 6 (4.2%) patients presented without any symptoms and 1 (0.7%) patient had attended a scheduled consultation at the neurosurgery service. Finally, a total of 47 (58.8%) patients presented with an active bleeding (rupture of AVMs), being holocranial headache the symptom from which these patients suffered the most. It was found that the onset of symptoms in general occurred between the late hours of the night and the first hours of the day, from 22:00 to 7:00 o´clock in the majority of patients (61.3%), which are the hours that are regularly not dedicated to work or school in our country. At symptom onset, most patients were asleep, resting at home, or waking up. (Table 1)

Relevant Past History

Among the comorbidities and predictors factors, the most common was the existence of previous cerebral intraparenchymal hemorrhage observed in 23 (28.7%) patients, followed by type 2 Diabetes Mellitus as the second most common comorbidity in 15 (18.8%) patients, and Systemic Arterial Hypertension in third place with 14 (17.5%) patients. Inquiring more about personal history, we found that almost half of our included patients led a sedentary lifestyle or were smokers (45% and 40%, respectively).

Outcome

For the architectural characteristics of the AVM, we found a median size of 10.29 cm^3 (2.49 cm^3 - 35.66 cm^3). Forty-one (51.2%) occurred in right side, being mainly found in the frontal lobe in 24 (30%) patients. The middle cerebral artery was the most common nutrient artery in 34 (32.1%) patients and in the venous system, the collateral veins of the superior sagittal system 21 (20.8%) were most commonly affected. For diagnosis and classification, CT scans were performed on the patients. For more detailed characteristics, consult Table 2.

For treatment, angio-embolism alone or accompanied by radiosurgery or surgical excision by craniotomy was the mostly used of all approaches in 41 (39.8%), followed by craniotomy in 37 (35.92%) and radiosurgery in 13 (12.6%), finally; a conservative approach was chosen in 12 (11.7%) patients, showing that the vast majority decided not to resort to expectant treatment. (Table 1)

It was found that a total volume in cubic centimeters greater than 9.18 cm^3, as well as the presence of more than one symptom, and a history of previous cerebral intraparenchymal hemorrhage, were significant predictors factors for mortality ($p< 0.05$), as shown in Table 3.

Figure 1 illustrates AVMs size as a predictor of mortality.

DISCUSSION.

In this retrospective study, we found that the average age of presentation is 26.8 years, with a slightly higher prevalence in the female sex; obesity, overweight as well as type 2 diabetes mellitus, systemic arterial hypertension and sedentary lifestyle were present in an important part of the population

Our findings differ from the data that was presented by the National Hospital of Neurology and Neurosurgery of Mexico,[20] who report an average age of presentation of 32.9 years and no predilection between men and women.[20] We also found that holocranial headache was the most common symptom which agrees with what was previously reported by Mariano Rinaldi in 2015.[21] Rinaldi not only found that holocranial headache was most commonly reported at symptom onset, but that 30.8% were classified as Spetzler-Martin class III. We found that 23.8% of our patients were a class III Spetzler-Martin. It has been reported that grades I and II have good results with microsurgery while grades III and IV mostly benefit from endovascular embolism, as shown in Mariano Rinaldi's study where 16 cases of grades III and IV required endovascular treatment prior to definitive surgical treatment. In our center, 68 subjects had a surgical approach, and at least 23 (33.8%) shared an approach through craniotomy and/or radiosurgery in addition to angio-embolism. These approaches are in accordance with AHA 2017 recommendations for AVMs Spetzler-Martin III and IV.[22]

We found other similarities to Rinaldi's previously reported results, such as the distribution of AVMs towards the right side and mainly in the frontal lobe, in 51.2% and 30% of cases, respectively. Another important aspect was the history of previous cerebral intraparenchymal hemorrhage (28.7%).[21]

An interesting finding in our study was regarding the pregnant women. According to what has been reported in the literature, we found that, although rare, AVMs are responsible for about 50% of subarachnoid hemorrhages in pregnant women and are the third cause of non-obstetric maternal mortality. However, there are discrepancies in the literature regarding the influence of pregnancy on the natural history of AVM. However, we did not find a higher risk in mortality for pregnant patients in our study. [23,24,25] In any case, it should be noted that the number of pregnant patients included was small.

Overall mortality in our sample of 80 patients was 17.5% (14 patients, 10 pediatrics and 4 adults). The mortality in pediatrics was 33.3% (10 patients out of 30).The mortality in adults was only 8% (4 patients out of 50). The mortality in the adult population is similar to that reported by Hillman, et al.[26] as well as other literature, such as Rinaldi et al.[21] who reported 13.46% mortality rate and other studies with a range from 10 to 15%.[17,20] However, the mortality in the pediatric population is vastly different from that of the literature, being 33.3% in our study and 12% in a study published by Riordan, et al.[27]

Finally, we note that hemorrhage is an important mortality factor; which was the most common presentation in our sample; occurring in 24 out of 30 pediatric patients, while in adults, it was present in 23 out of 50.

Mortality in bleeding adults was 17% and in bleeding children was almost 42%. High rates of bleeding in pediatrics could explain their high mortality rates. While in adults, mortality in ruptured AVMs does approach the 10-20% ratio, which is reported by other authors.[28,29]

It is interesting that the chronobiology of AVM's rupture is not actually described in the literature, but it has been seen that in children the onset of symptoms can generally be found in the morning hours; regardless of their daily activities and waking up time.[30,31 32] The aforementioned has been highlighted as a poor prognostic factor in both children and adults, without being correctly demonstrated by the literature.[30-36] In our study we found a

high prevalence of symptom onset in non-laboral hours, but a future and more specific analysis focusing on this exact variable is necessary.

Limitations

The main limitation of this study is that it is retrospective in nature. More ambispective and prospective studies are necessary in order to identify other potential predictors factors. Another limitation is that, due to the patient privacy rules of our hospital, patient files can only be kept for five years after their last visit, thus no information is available for previous years. Other limitations encountered include that perhaps not all the AVMs were reported, because clinical records reviewed are not always filled with reliable data. This data can also be corrected by doing a prospective study, establishing a time of 5 years and comparing the differences between them.

Conclusions

Determining the chronobiology of AVMs, would work to find a variant of good or bad prognosis or orient the clinical diagnosis in search of differential diagnoses in an emergency situation as it should be considered as an interesting and relatively easy variable to determine with the appropriate and targeted approach in the near future. In Mexico, there are no studies comparing pediatric and adult populations and there are few studies focusing on AVMs in general, it is therefore important to emphasize the importance of these pathologies, since they are considered silent but deadly when they present active bleeding. In this paper, we clearly illustrate the relation between mortality and age, and also find that although AVMs are more common in adults, there is a lesser mortality in this group. Determining the epidemiological characteristics of the country's large tertiary care centers could serve as a milestone for more focused and useful research to understand the pathogenesis, prevention and extent of AVMs.

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1 **FIGURES AND TABLES.**

2 **Table 1. General characteristics population characteristics.**

Variable	N = 80 (%)
Female gender	45 (56.3)
Age in years †	26.9 ± 17.5
Symptomatology	**N = 142 (%)**
Holocranial headache	34 (23.9)
Tonic-Clonic Seizures	29 (20.4)
Loss of Consciousness	24 (16.9)
Hemibody paralysis	10 (7.0)
Vomiting	9 (6.3)
Asymptomatic	6 (4.2)
Hemicranial headache	5 (3.5)
Aphasia	4 (2.8)
Other	21 (14.8)
Comorbidities and Predictors	**N = 80 (%)**
Diabetes	15 (18.8)
Hypertension	14 (17.5)
Cancer	2 (2.5)
BMI	
Obesity (> 30)	37 (46.3)
Overweight (25 - 29.9)	32 (40.0)
Normal weight (18.5 - 24.9)	11 (13.8)
Smoker	32 (40.0)
Sedentary lifestyle	36 (45.0)
Pregnancy	3 (3.8)
Event characteristics	**N = 80 (%)**
Temporality	
22:00 - 7:00	49 (61.3)
7:01 – 21:59	31 (38.8)
Place or action of the patient	
Asleep	22 (27.5)
House	16 (20.0)
Waking up	12 (15.0)
Elective consultation	11 (13.8)
Working, school	9 (11.3)
Showering	6 (7.5)
Exercising	3 (3.8)
Street	1 (1.3)
Hemorrhage	**N = 80 (%)**
All-age hemorrhage	47/80 (58.8)
Pediatric hemorrhage (0 -17 years)	24/30 (80.0)
Adult hemorrhage (≥18 years)	23/50 (46.0)
Previous hemorrhage	23 (28.7)
Posterior hemorrhage	10 (12.5)
Treatment used	**N = 103 (%)**
Angio-embolism	41 (39.8)
Surgical excision by craniotomy	37 (35.9)
Radiosurgery	13 (12.6)
Conservative management	12 (11.7)
Mortality	**N (%)**
All-age mortality	14/80 (17.5)
Pediatric mortality (0-17 years)	10/30 (33.3)
Mortality in adults (≥18 years)	4/50 (8.0)

† Represents the use of the mean and standard deviation to represent the data.

1

2 **Table 2. Characteristics of arteriovenous malformations.**

Laterality	**N = 80 (%)**
Right	41 (51.2)
Left	37 (46.3)
Bilateral	2 (2.5)
Cerebral location	**N = 80 (%)**
Frontal	24 (30.0)
Occipital	15 (18.8)
Temporary	12 (15.0)
Frontoparietal	8 (10.0)
Frontotemporal	6 (7.5)
Parietal	3 (3.8)
Cerebellum	3 (3.8)
Other	9 (11.3)
Nutritional arteries	**N = 106 (%)**
Deep middle cerebral artery	34 (32.1)
Deep posterior cerebral artery	28 (26.4)
Deep anterior cerebral artery	27 (25.5)
Posterior inferior cerebellar artery	8 (7.5)
Internal carotid artery	8 (7.5)
Middle meningeal artery	1 (0.9)
Venous drainage	**N = 101 (%)**
Collaterals of the superior sagittal sinus	21 (20.8)
Vein of Galen	14 (13.9)
Deep circulation	10 (9.9)
Superior longitudinal sinus	8 (7.9)
Internal cerebral vein	8 (7.9)
Superficial cerebral veins	8 (7.9)
Other	32 (31.7)
Spetzler-Martin arteriovenous malformation grading system	
I	7 (8.8)
II	37 (46.3)
III	19 (23.8)
IV-VI	17 (21.3)
Note: Spetzler -Martin VI is not used in our center	

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1 **Table 3. Odds ratio of the analyzed variables as predictors of mortality**.
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	OR 95% CI	P
AVM size		
Total Volume (cm3)		
<9.2 cm	0.063 (0.008 - 0.519)	0.010
> 9.2 cm	16.00 (1.926 - 132-899)	0.010
Length		
<3.4 cm	0.150 (0.042 - 0.539)	0.004
> 3.4 cm	6.667 (1.854 – 23.973)	0.004
Width		
<1.9 cm	0.077 (0.010 - 0.622)	0.016
> 1.9 cm	13.00 (1.607 - 105.146)	0.016
Depth		
<1.8 cm	0.053 (0.006 - 0.439)	0.007
> 1.8 cm	18.947 (2.276 - 157-757)	0.007
Number of symptoms		
≤1 symptom	0.242 (0.062 - 0.946)	0.041
> 1 symptom	4.022 (1.026 – 15.467)	0.041
Hemorrhage		
Previous hemorrhage	4.533 (1.359 – 15.126)	0.014
Current hemorrhage	12.235 (1.513 – 98.966)	0.019
Posterior hemorrhage	2.299 (0.514 - 10.280)	0.276
Laterality		
Left	1.192 (0.579 - 6.318)	0.288
Right	0.590 (0.179 - 1.950)	0.387
Bilateral	5.33 (0.683 - 41.622)	0.110
Age		
≤ 17 years	5,750 (1.610 – 20.553)	0.007
≥18 years	0.174 (0.049 - 0.621)	0.007
Sex		
Female	0.737 (0.232 - 2.341)	0.605
Male	1.357 (0.427 - 4.311)	0.605

An odds ratio with a 95% confidence interval greater than 1 was interpreted as a clinically significants predictors. On the contrary, a 95% confidence interval value less than 1 was interpreted as a clinically significant protective factor. A p value less than 0.05 was interpreted as statistically significant. Note: OR = Odds Ratio. CI = Confidence Interval.

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Figure 1. Receiver operator curve of arteriovenous malformation size as a predictor for mortality.