Title: **Is the determination of venous ectasia relevant for the treatment of brain arteriovenous malformation?**

**Other options of title:**

1) Interobserver and intraobserver variability in the assessment of dilated veins: 57 cases of brain arteriovenous malformation treated by the endovascular venous approach.

2) Angiographic evaluation of interobserver agreement for dilated veins in 57 cases of brain AVMs treated by a venous approach.

3) Angiographic evaluation of interobserver agreement for dilated veins in brain AVMs. A study of 57 cases that were embolized by the venous approach.

4)Interobserver and intraobserver variability in the assessment of dilated veins: 57 cases of brain AVM treated by the endovascular venous approach.

Abstract:

**Introduction:**

Brain AVMs are congenital lesions with atypical vascular shunts in the central nervous system, which involve a connection between one or multiple feeding arteries and draining veins that bypass the normal capillary.1

The incidence of brain AVMs is estimated at approximately 1 per 100 000 per year in unselected populations, and the point prevalence in adults is 18 per 100 000, with a mean age at diagnosis of around 35 years, affecting both sexes equally.2,3,4 The condition is usually discovered in the diagnosis of intracranial hemorrhage, epilepsy, chronic headache, and focal neurologic deficits without any bleeding correlation.

Brain AVMs are usually associated with angio-architectural risk factors for hemorrhage. These include age, associated aneurysm, venous outflow stenosis, AVM size, AVM location, and deep venous drainage.5,6,7 Impairment of the venous drainage of an AVM is significantly associated with the risk of hemorrhage.8,9

Currently, there are three different alternatives for the treatment of brain AVMs: neurosurgery, radiosurgery, and endovascular treatment. Regardless of the choice, treatment is generally complex and could be multidisciplinary.2

This study was a retrospective angiographic analysis of venous ectasia in the brain AVMs of patients, who were embolized by the endovascular technique. At least one session was conducted using the transvenous approach, and the results of intercorrelations between interpretations were considered in determining implications for the treatment of brain AVMs.

**Materials and Methods:**

**Patient Demographics and Clinical Presentation**

This Institutional Review Board of our University Hospital, at Limoges France, approved this study. Informed consent was obtained from all patients before the intervention. We retrospectively evaluated the medical records of 57 patients with intracranial AVM, who underwent endovascular treatment (at least one session via the venous approach), between February 2008 and July 2019. This study was focused on the analysis of venous ectasia, and the sample was independently reviewed by three senior interventional neuroradiologists.

The analysis of dilated veins was performed by a rigorous selection of digital subtraction angiograms, which were obtained for each patient immediately before treatment. The parameter adopted to evaluate the dilated veins, was the referential pattern of the vessel, which was two times smaller than the contralateral side. The images were shown to the evaluators in a questionnaire that included all of the selected images. The evaluators were allowed around 2 min for each answer. They were isolated during the survey, and they were not allowed to confer among themselves during the analysis of the images.

For all evaluators, differences in proportions were assessed using the Fisher’s exact test, to determine correlations between dilated veins and hemorrhage complications. Each analysis was individualized, comparing whether the evaluations showed significance or not.

Interobserver agreement between the interventional neuroradiologists on the interpretation of images was measured using the kappa statistic test, based on the answers of each, following the questionnaire.

**Statistical Analysis**

The R® version 3.6.1 package for Mac®, 2019 and the Microsoft Excel® software package for Mac®, 2019 software were used for statistical analysis. Descriptive analysis was used to characterize the sample. Quantitative variables were expressed as mean ± standard deviation (SD). Qualitative variables were expressed as frequency and percentage values. The Fisher’s exact test (two-sided) was used to compare categorical variables (univariate analysis).

The kappa statistic test was used to analyze categorical agreement between the observers. The values for interobserver ratings were reflective of the agreement among the evaluators in determining whether the veins were dilated or not. Those values were defined as <0.4, slight agreement; 0.41-0.8, moderate agreement; and >0.81, very good agreement. The association between variables was considered significant when the P-value was <.05.

**Results**

***Description of data***

The mean age of the 57 patients treated was 38.5 years (range, 9-78 years), and the sample included 28 females and 29 males. The initial clinical presentation was secondary to rupture and bleeding in 38 patients (66%). Of the 57 AVMs treated, 37 (64.9%) had just one venous collector, 18 (31.6%) had two collectors, and 2 (3.5%) had more than three collectors.

Among the sample of 57 patients, 21 (37%) lesions were located in the left hemisphere, 15 (26.5%) in the right cerebral hemisphere, one (1.5%) in the corpus callosum, six (10.5%) in the thalamus, three (5%) in the mesencephalon, one (1.5%) was commissural, five (9%) were in the striatum, and five (9%) in the cerebellum ***(Table 1)***. Deep venous drainage was present in 16 (28%) AVMs. According to the Spetzler–Martin classification, the 57 AVMs were classified as grade I, five (9%); II, 18 (31.5%); III, 23 (40.5%); IV, 10 (17.5%); and V, one (1.5%) ***(Table 2)***. The patients analyzed were embolized by the venous approach in at least one session. The number of patients treated in just one session was 31 (55%); in two sessions, 16 (28.5%); three sessions, four (7%); four sessions, two (3%); five sessions, three (5%); and just one patient (1.5%) was treated in six sessions.

**Table 1**. Localization of brain AVM treated with a transvenous approach

|  |  |
| --- | --- |
| Locations of brain AVM |  |
| *Location* | *No. (%)* |
| *Hemisphere*  Right  Left  *Commissural*  *Deep brain*  Corpus Callosum  Thalamus  Striatum  *Brain stem*  Mesencephalon  *Cerebellum* | 21 (37)  15 (26.5)  1 (1.5)  1 (1.5)  6 (10.5)  5 (9)  3 (5)  5 (9) |



**Table 2.** Spetzler–Martin classification of the 54 AVMs treated

|  |  |
| --- | --- |
| Spetzler–Martin Grade | *No. (%)* |
| **I**  **II**  **III**  **IV**  **V** | **5 (9.0)**  **18 (31.5)**  **23 (40.5)**  **10 (17.5)** |

**Intraobserver and Interobserver Agreement**

After the questionnaire was completed by the evaluators, the results of their analyses of dilated veins differed. Regarding their findings of the dilated veins, the first evaluator had a total of 24 cases (42.1%); the second evaluator had 28 (49.1%); and the third evaluator had 36 (63.1%). Among all evaluators, the number of hemorrhagic complications associated with dilated veins were observed in eight patients (14%), among which, six (10.5%) showed dilated veins.

The correlation between dilated veins and hemorrhage complications were determined by the Fisher’s exact test in each of the three analyses. After the findings of the evaluators were compared, no significant correlation with bleeding complications was observed. The results of all three evaluators showed a P-value >.05, with a corresponding odds ratio and confidence interval, showing no significant differences ***(Table 3*)**. Consistent with these findings, when the Fisher’s test was applied to determine the correlation between the absence of dilated veins and previous rupture, the results of all evaluators were significant. Considered separately, P=0.001 was observed for the first evaluator, P=0.01 for the second, and P=0.004 for the third ***(Table 4)***.

**Table 3.** Fisher’s test analysis among all evaluators, relating to dilated veins and hemorrhage risk factors

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  |  |
| ***Evaluator 1***  ***Evaluator 2***  ***Evaluator 3*** | ***P-value***  .06  .14  .70 | ***Odds ratio***  5.0161  3.6016  1.8801 | ***Confidence interval (%)***  0.78-55.87  0.57-39.94  0.29-20.91 |

**Table 4**. Fisher’s test analysis among all evaluators, relating to the lack of dilated veins and AVM previous rupture risk

|  |  |  |  |
| --- | --- | --- | --- |
| *Evaluator 1* | ***P-value***  .001 | ***Odds Ratio***  0.1331 | ***Confidence interval (%)***  0.029-0.51 |
| *Evaluator 2* | .012 | 0.2145 | 0.049-0.79 |
| *Evaluator 3* | .004 | 0.1217 | 0.012-0.62 |

Among the sample of 57 patients, only a few cases showed dilated veins (Figure 1), for which the evaluators were all in agreement. However, in some cases, the findings were divergent (Figure 2), and the kappa statistic test was applied. This statistic determined whether the combination of answers in the interobserver analysis was well employed.

The kappa statistic test combined the findings between two evaluators separately, and those combinations showed moderate agreement, K (0.41-0.8). The first combination was between the findings of Evaluators 1 and 2, for which K was 0.5074. This was then compared with the findings of Evaluators 1 with 3, for which K was 0.4610. The last comparison considered the second and the third evaluators, for which K was 0.4412.

**Figure 1) *1) CASE:*** *37)* S.G.H, 29, M, A and B, anteroposterior and lateral views, respectively, of an internal carotid artery injection, showing the venous time with well visualized dilated **right parietal cortical vein;** C, projection of the venous approach; D, super-selective venous injection via a microcatheter. ***2) CASE: 29 )*** G.S, 51, M, E and F, anteroposterior and lateral views, respectively, of an internal carotid artery injection, showing the venous time with well visualized dilated **right frontal cortical vein;** G, projection of the venous approach; H, super-selective venous injection via a microcatheter. ***3) CASE: 18 )*** F.M, I and J, anteroposterior and lateral views, respectively, of an internal carotid artery injection, showing the venous time with well visualized dilated **right parietal vein**; K, projection of the venous approach; L, super-selective venous injection via a microcatheter.

***Uma imagem contendo grama, foto

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**Figure 2) *1) CASE: 12 )*** L.R, 64, M, A and B, anteroposterior and lateral views, respectively, of an internal carotid artery injection, showing the venous time with well visualized normal **frontal cortical vein;** C, projection of the venous approach; D, super-selective venous injection via a microcatheter. ***2) CASE: 29 )*** G.S, 51, M, E and F, anteroposterior and lateral views, respectively, of an internal carotid artery injection, showing the venous time with well visualized dilated **frontal cortical vein;** G, projection of the venous approach; H, super-selective venous injection via a microcatheter. ***3) CASE: 18 )*** F.M, I and J, anteroposterior and lateral views, respectively, of an internal carotid artery injection, showing the venous time with well visualized dilated **frontal cortical vein;** K, projection of the venous approach; L, super-selective venous injection via a microcatheter.

**Discussion**

Intracranial AVMs are a cerebrovascular pathology that have a cumulative risk of functional disability or death, due to intracranial bleeding and refractory epilepsy. Moreover, intracranial AVMs may also be asymptomatic for extended periods or never manifest any clinical symptoms.

The treatment of brain AVMs is complex and may involve different techniques, such as endovascular embolization (basically transarterial and transvenous approaches), neurosurgery, radiosurgery, and sometimes a combination of two or more of these techniques.2

The development and rupture of AVMs is a multifactorial and multistage process. This should be considered, as an impairment of embryonic vasculogenesis can be correlated with other phenomena associated with the characteristics of brain AVM angioarchitecture that are conducive to hemodynamic changes.10,11,12

Angioarchitecture refers to the morphology of internal structures and other characteristics of the blood vessels.13 To understand such anatomy is often difficult because of the entanglement of the vessels, which comprise a nidus and the surrounding arteries and veins, resulting in one aspect of anamorphosis.14 A precise recognition of the different components of brain AVM angioarchitecture has considerable importance in the treatment plan, can reduce the number of complications associated with the procedure, and could aid in anticipating treatment outcome in some cases, to avoid possible rupture. This is especially so in cases with characteristics that are correlated with hemorrhage, such as those with deep venous drainage, intranidal aneurysm, increased size of the nidus, stenotic venous drainage, and specific AVM location.13,15,16,17 Our goal was to emphasize the dilated veins as an important factor to be identified before selecting any patient for the treatment of intracranial AVM.

All evaluators used the same method to determine whether the vein was dilated or not. The principal vein collector nearest the nidus was compared with a vein of normal size with similar topography on the contralateral side. This difference should have been double the “normal” size to be considered dilated. In the sample of 57 patients, we observed dilated veins (Figure 1) for which evaluators shared no doubts and there was a consensus for all. However, in other cases, the findings were divergent (Figure 2), and the kappa statistic test was applied to determine the combination of answers that was employed in the interobserver analysis.

The term angiomatous change was defined by Marks et al.,15 as representing multiple dilated vessels that feed and are recruited by the AVM nidus, which consists of arterioles that shunt directly into venous loops in a passive vascular system, in which the rate of blood flow is pressure dependent.15,18 The angiomatous aspect is evident when the pressure of the arterial pedicle or the venous collector is not regular. This means that in an AVM, for which the arterial feeder has low pressure, the nidus needs to recruit other feeders, such as the cortical branches, to normalize the pressure, and this reversal of pressure gradient increases the incidence of hemorrhage.15

In a similar manner, if an AVM has a collector vein that is not dilated, the pressure becomes higher than normal. Consistent with this point of view, Nornes and Grip19 showed that flow is directly related to the reduction in pressure along the length of a tube (according to the equation of Poiseuille/Hagenbach). This equation means that the pressure reduction along the length of a tube and the pressure on the vessels of an AVM nidus are directly related to the length of the artery supplying the AVM.15,19

When we microscopically analyze the walls of the vein in a ruptured AVM, there are few alterations that are evident, which are the results of mechanical impact disorders, caused by changes in hemodynamic flow into the angioarchitecture.10 Researchers have found that the preferred orientation of collagen fibers is in the direction of vessel stretch.20 The normal arrangement of collagen fibers is a symmetric spiral. However, as the disease progresses, this configuration is often altered. The turbulence disturbs the direction of flexibility of the vessel wall and the effects of stretch. This could further lead to a disordered arrangement of collagen fibers and weakness.10 The main cause of fragility of the vessel wall could be fibrous repair, which often results in hyperplasia of type I and Type III collagen with disordered arrangement. The advantage of this process is that it fills in the defects, and maintains the integrity of the vessel wall, which are adaptations to the disease.10

Our results showed no significant correlation between dilated veins and hemorrhagic complications, both during and after the transvenous approach. We analyzed the images of the veins immediately before the procedure **(Table 3).** Even if we considered the hemodynamics and pathological alterations as the typical physiopathology of AVM, our results would remain the same. Therefore, the dilated vein is an adaptation of the disease and part of its progressive evolution.

On the other hand, when the Fisher’s test was used to compare both the undilated veins and previous rupture among each evaluator, we was found significant differences for all analyses **(Table 4).** Therefore, if we take into account our statistical results and what has already been described about brain AVM physiopathology in the literature, we could deduce a causal link to highlight our hypothesis. We infer that the presence of dilated veins serve as a protective factor against spontaneous rupture.

Limitations of the study

The present study was subject to limitations due to the small number of cases. The sample represented cases at a single center that employed curative embolization strategies for AVMs, and at least one session using the transvenous approach. This strategy consequently decreased the sample size. The data analysis was done retrospectively. The images could have been analyzed using the protocols of 4D injections21 and reconstructions facilitated by the Siemens® software, to better define the size and number of the veins that were nearest to the nidus. This method is usually used during AVM embolization at our facility. However, one of the purposes of this study was to determine the angioarchitecture using digital subtraction angiograms as a useful tool, especially for facilities that are not equipped with 4D technology, and correctly select the appropriate brain AVM cases for treatment.

We identified that dilated veins are an important consideration in patients with brain AVMs, that can facilitate treatment decisions. Our research team intends to conduct further research into AVM treatments.

**Conclusion**

The advent of novel technologies in the neurointerventional field [increasingly](https://www.linguee.com/english-portuguese/translation/increasingly.html) contributes to the development of treatment options for brain AVM. The complex physiopathology makes the discovery of such options even more challenging, which is why new information about the disease is extremely important. Our statistical analysis showed that venous ectasia in a brain AVM supports the idea of its role as a protective factor against spontaneous rupture. As with other novel studies, multicentric and larger clinical case series will be needed to determine the reproducibility and validation of potential benefits.

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