Arteriovenous Malformations: Congenital or Acquired Lesions?

Anastasia Tasiou[1], Christos Tzerefos[1], Cargill H. Alleyne Jr.[2], Edoardo Boccardi[3], Bengt Karlsson[4], Neil Kitchen[5], Robert F. Spetzler[6], Christos M. Tolias[7], Kostas N. Fountas[1]

■ OBJECTIVE: **Arteriovenous malformations (AVMs) were believed to be congenital. However, an increasing number of de novo AVM cases have questioned this doctrine.**

■ METHODS: **A consensus meeting of international experts attempted to establish a consensus on the nature of these relatively rare but challenging vascular lesions. In addition, an extensive search of the subject was performed using the PubMed medical database.**

■ RESULTS: **All participants agreed that genetic factors may play a role in the pathogenesis of AVMs. All but 1 participant believed that an underlying genetic predisposition may be detected later on in a patient's life, whereas genetic variations may contribute to sporadic AVM formation. The presence of genetic variations alone may not be enough for an AVM formation. A second hit is probably required. This consensus opinion is also supported by our literature search.**

■ CONCLUSIONS: **We discuss the literature on the genetics of AVMs and compare it with the consensus meeting outcomes. The congenital or noncongenital character of intracranial AVMs has an impact on the understanding their biological behavior, as well as their efficient short-term and long-term management.**

INTRODUCTION

Cerebral arteriovenous malformation (AVM) refers to a tangle of abnormally connected arteries and veins, forming a network of arteriovenous shunts, without an intervening capillary bed. For many years, AVMs had been considered to be congenital.[1-6] By definition, congenital is a lesion present at birth even although it may be discovered later in life. Brain AVMs occur in families with hereditary hemorrhagic telangiectasia (HHT) or hereditary neurocutaneous angiomatosis.[7,8] Moreover, a few familial cerebral AVMs have been reported in patients with the RASA1 gene mutation.[9] However, families without hereditary diseases have been described to have ≥2 affected relatives. Familial cerebral AVM is defined as the occurrence of an AVM in ≥2 relatives (up to third degree) in a family without hereditary disorders.[10] Thus, genetic factors may play a role in the pathogenesis of AVMs.[11-13] In addition, recent genetic analysis studies have clearly shown that certain single nucleotide polymorphisms in the NOTCH4 gene are associated with certain sporadic AVM genotypes but also with the hemorrhage rates.[14] It has been previously postulated that familiar AVMs differ from sporadic ones regarding their formation and their clinical phenotype, as well as their molecular behavior.[9,15]

An increasing number of cases of de novo AVM formation have put into question the notion that AVMs are congenital. According to the pertinent literature, many cases are diagnosed in adults without being present at birth, supporting the predisposition that they constitute acquired lesions.[16-18] On the other hand, AVM recurrence may occur after complete extirpation of the initial lesion (confirmed by postoperative digital subtraction angiography [DSA]). This phenomenon has been mostly described in pediatric populations.[5,19-24] Thus, Karlsson et al.[25] believe that AVMs are developmental rather than congenital malformations and develop as long as the brain matures (i.e., until the age of 25 years). In an earlier study applying a mathematical model for calculating the AVM-associated risk of hemorrhage by Karlsson et al., it was assumed that AVMs are congenital. However, if this were the case, the risk for hemorrhage should have been increasing every

Key words
- Acquired lesions
- Cerebral arteriovenous malformations
- Congenital lesions
- De novo formation
- Socioeconomic ramifications

Abbreviations and Acronyms
AVM: Arteriovenous malformation
DSA: Digital subtraction angiography
HHT: Hereditary hemorrhagic telangiectasia

From the [1]Department of Neurosurgery, University Hospital of Larissa, School of Medicine, University of Thessaly, Larissa, Greece; [2]University Neuroscience Augusta Back, Augusta, Georgia, USA; [3]Department of Diagnostic and Interventional Neuroradiology, Niguarda Hospital, Milan, Italy; [4]Department of Surgery, Division of Neurosurgery, National University Hospital, Singapore; [5]Victor Horsley Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom; [6]Department of Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona, USA; and [7]Department of Neurovascular Surgery, Kings College Hospital, London, United Kingdom

To whom correspondence should be addressed: Anastasia Tasiou, M.D., Ph.D. [E-mail: ttasiou@yahoo.com]

Citation: World Neurosurg. (2020) 134:e799-e807.
https://doi.org/10.1016/j.wneu.2019.11.001

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

1878-8750/$ - see front matter

Table 1. A Total of 43 Full-Text Articles, Referring to De Novo Arteriovenous Malformation Formation Case Reports, Included in Our Literature Search

	Reference	Cases (n)	Status
1	Akimoto et al., 2003[19]	1	PubMed search
2	Alvarez et al., 2012[34]	1	PubMed search
3	Bai et al., 2012[35]	1	PubMed search
4	Bulsara et al., 2002[36]	1	PubMed search
5	Dogan et al., 2019[37]	1	PubMed search
6	Friedman et al., 2000[38]	1	Reference screening
7	Fujimura et al., 2014[39]	1	PubMed search
8	Fuse et al., 2001[40]	1	Reference screening
9	Gonzalez et al., 2005[23]	1	PubMed search
10	Harris et al., 2000[41]	1	Reference screening
11	Jeffree and Stoodley, 2009[42]	3	Reference screening
12	Kilbourn et al., 2014[43]	1	PubMed search
13	Koch et al., 2016[44]	1	PubMed search
14	Krayenbühl, 1977[45]	1	Reference screening
15	Lo Presti et al., 2018[46]	1	PubMed search
16	Lv and Wang, 2018[47]	1	PubMed search
17	Mahajan et al., 2009[48]	1	PubMed search
18	Markham and Hollingworth, 2015[49]	1	Reference screening
19	Mathon et al., 2013[50]	1	PubMed search
20	McKinney et al., 2008[51]	1	PubMed search
21	Mendelow et al., 1987[52]	1	Reference screening
22	Miller et al., 2014[53]	1	PubMed search
23	Miyasaka et al., 2003[54]	1	Reference screening
24	Morales-Valero et al., 2014[17]	2	Reference screening
25	Morioka et al., 1988[55]	1	Reference screening
26	Nakamura et al., 2016[56]	1	PubMed search
27	Neil et al., 2014[57]	1	PubMed search
28	Nussbaum et al., 1998[58]	1	Reference screening
29	O'Shaughnessy et al., 2005[24]	1	PubMed search
30	Ozsarac et al., 2012[59]	1	PubMed search
31	Pabaney et al., 2016[60]	1	PubMed search
32	Peeters, 1982[61]	1	Reference screening
33	Porter and Bull, 1969[1]	1	Reference screening
34	Rodriguez Arias et al., 2000[62]	1	Reference screening
35	Santos et al., 2018[63]	1	PubMed search
36	Schmit et al., 1996[64]	1	Reference screening
37	Shi et al., 2017[65]	2	PubMed search
38	Shidoh et al., 2017[66]	1	PubMed search
39	Shimoda et al., 2016[67]	1	PubMed search
40	Song et al., 2007[68]	1	Reference screening
41	Stevens et al., 2009[69]	1	PubMed search
42	Wu et al., 2014[70]	1	PubMed search
43	Yeo et al., 2014[71]	2	PubMed search

year, resulting in unrealistically high hemorrhage risks for elderly patients, which is not observed.[26]

Although AVMs are rare, they constitute the leading cause of hemorrhagic stroke in children and young adults.[27-33] Individuals harboring AVMs are subjected to lifelong risk of morbidity and mortality.[27-32] The issue of the nature of cerebral AVMs remains controversial. However, it is of paramount importance to unravel the natural history of these lesions for a better understanding of their biological behavior and proper long-term management, as well as for their socioeconomic ramifications.

In this article, we attempt to establish a consensus on the nature of these rare but challenging vascular lesions.

METHODS

An extensive search of the PubMed medical database was performed using the terms "arteriovenous malformations," "cerebral arteriovenous malformations," "intracranial arteriovenous malformations," "AVMs," "brain AVMs," "de novo," "sporadic," and "acquired," in all their possible combinations. The search was limited to articles in English, and only in series of human patients. In addition, the references of the retrieved articles were meticulously reviewed for any additional articles of interest. Special attention was paid to avoiding repetition of clinical data from overlapping series, published in different journals or at different times. However, such redundancies cannot be ruled out.

In March 2019, a consensus meeting on the natural history of brain AVMs, involving worldwide experts on AVM management, was held in Athens, Greece. There were 3 main questions: 1) Are AVMs congenital or acquired lesions?; 2) Are AVMs present at birth?; and 3) Does that have any impact on the overall management of patients harboring AVMs?.

RESULTS

Literature Data

A total of 91 articles were identified by our literature search. Sixty-two were excluded on the basis of the title and abstract screening. Twenty-nine records without duplications and/or repetition of data from overlapping series were screened for eligibility. In addition, 16 studies were added after meticulous review of the references of the retrieved articles. Forty-three full-text articles, referring to de novo AVM formation case reports (48 cases), met our inclusion criteria (Table 1). A summation of our literature search data is shown in Figure 1.

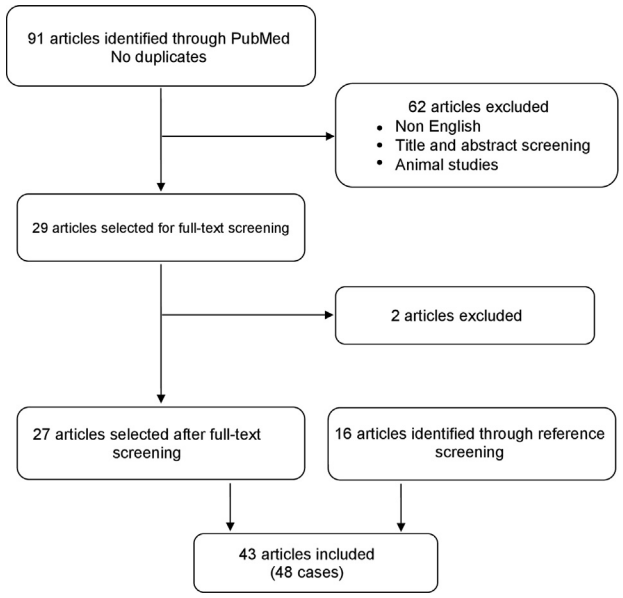

Figure 1. Indicative flowchart of our literature search data.

According to the pertinent literature, AVMs have been described in families with HHT, cavernous malformation—AVM familial lesions, or hereditary neurocutaneous angiomatous malformations.[9] However, there is an increasing body of evidence, including animal model and clinical data, that AVM formation may involve an interaction between genetic susceptibility and environmental/acquired factors.[15] Therefore, it is believed that the presence of a genetic abnormality alone is not enough to trigger AVM formation, and thus, a second hit is required. This second hit may well be an environmental factor such as a hypoxic insult, trauma, radiation exposure, epilepsy, an inflammatory process, a neuronal migration disorder, hydrocephalus, or a hormonal disturbance.[15] This second hit induces angiogenesis through various different mechanisms including vascular endothelial growth and vessel sprouting through upregulation of vascular endothelial growth factor and hypoxia-inducible growth factor 1α.[15] This process is followed by a stabilization phase, during which vascular pericytes differentiate into smooth muscles cells via upregulation of endothelial platelet-derived factors, such as factor-sz and factor-sz1.[15] Furthermore, several previously reported animal models support the theory of an external second hit in genetically predisposed animals. Hence, the increasing number of documented cases of de novo AVM formation postulates that most AVMs are sporadic, supporting the theory that most of these lesions may form after birth.

Consensus Statements

The main question posed in our consensus meeting was if AVMs are congenital or acquired lesions. All participants agreed that genetic factors might play a role in the pathogenesis of AVMs. Most of the authors (all but one) believe that there may be an underlying genetic predisposition, which may become detectable later. Genetic variations may contribute to sporadic AVM risk. However, genetic susceptibility alone is not enough. A combination of environmental factors, the so-called second hit in the setting of gene abnormalities, is required for the formation of an AVM. Two of the participants strongly believe that the theory of AVMs being congenital lesions is a myth. One of them supports that AVMs are developmental lesions and develop until the age of 25 years, when the cerebral vasculature becomes mature. The opinion of all participants regarding the presence of AVMs at birth was that AVMs may not be present at birth and may develop later in life.

Regarding the third question about the importance of defining the congenital character of intracranial AVMs, all participants affirmed that this definition is of paramount importance for understanding the biological behavior, the natural history, and their overall outcome. It is also important for socioeconomic purposes and mostly for reimbursement issues raised by the patients' insurance companies. All emphasized that the main goal is to treat and do no harm, focusing on the fact that AVMs are rare, heterogeneous, and often complex lesions, which require a multidisciplinary approach.

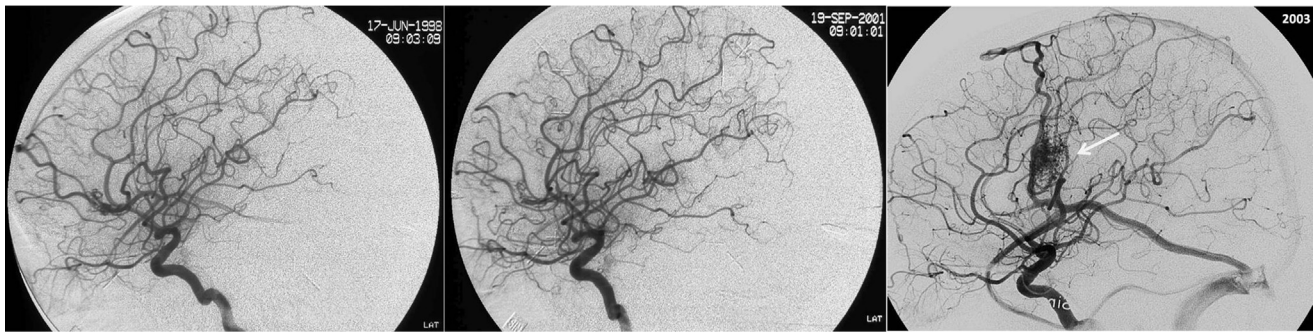

Figure 2. Digital subtraction angiography images of a 53-year-old woman with hemorrhage caused by a ruptured frontal lobe arteriovenous malformation. The patient underwent stereotactic radiosurgery via Gamma Knife twice, in 1998 and 2001. In 2003, the follow-up digital subtraction angiography showed a de novo arteriovenous malformation formation (*arrow*). (With the permission of Dr. Michael Söderman.)

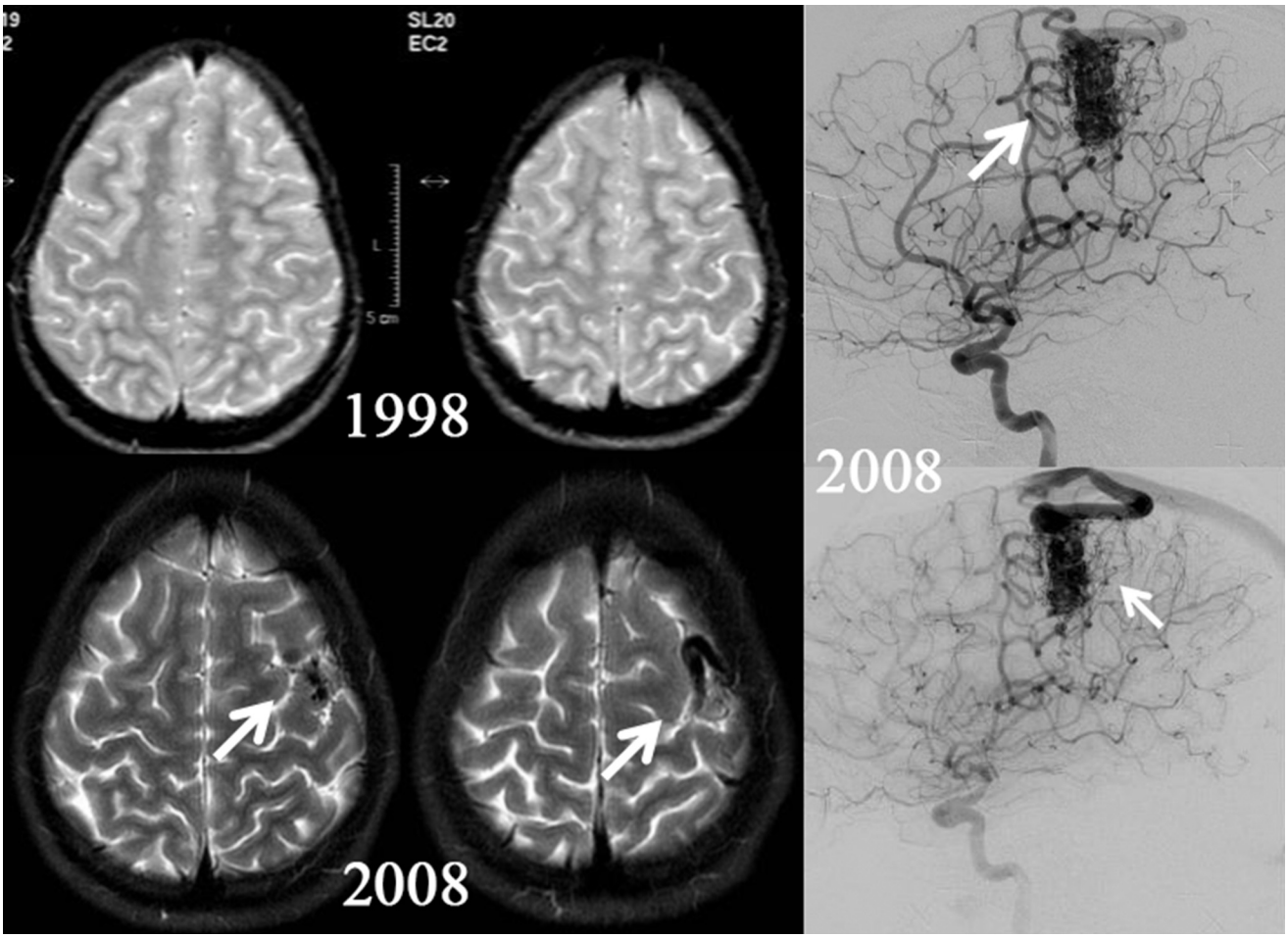

Figure 3. Brain magnetic resonance imaging of a 12-year-old girl showing no disease (1998). Repeated magnetic resonance imaging 10 years later (2008) showing a de novo arteriovenous malformation formation (*arrows*).

DISCUSSION

The AVM Congenital Doctrine

AVMs constitute a rare but important pathologic entity, and this is the most common cause of hemorrhagic stroke in children and young adults.[27-32] Moreover, AVMs are characterized by heterogeneity and complexity and are associated with a different clinical presentation and most likely different outcome. It has been estimated that the lifelong morbidity and mortality are as high as 35% and 29%, respectively.[27,72]

AVMs have been described in families with HHT, an autosomal dominant disorder.[7] AVMs in HHT are similar to the sporadic lesions and cannot be distinguished individually on the basis of their angioarchitecture. Furthermore, brain AVMs occur in families with hereditary neurocutaneous angiomatosis.[8] Di Rocco and Tamburrini in 2006 stated that brain AVMs were associated with a large port-wine stain birthmark on the forehead in patients with Sturge-Weber syndrome.[73] On the other hand, in Wyburn-Mason syndrome, a nonhereditary disorder, AVMs are associated with retinal angiomas.[74] Families without hereditary diseases have also been described to have $\geq$2 affected relatives. Familial cerebral AVM is defined as the occurrence of an AVM in $\geq$2 relatives (up to third degree) in a family without hereditary disorders.[10] Thus, genetic factors may play a role in the development of AVMs.[11,12] In 2007, van Beijnum et al. identified 25 families (53 patients) harboring brain AVMs.[10] These investigators concluded that it remains unclear whether the described families indicate true familial occurrence or represent accidental aggregation.[10]

De Novo Formation

In the pertinent literature, there is an increasing number of reported de novo cerebral AVMs.[1,17,19,23,24,34-71] The number of AVMs diagnosed in the neonatal period is limited.[75] It has been reported that only 1% of these lesions are identified during the first 2 years of life.[75] In 1996, Mullan et al. considered that AVMs originate early during embryonic development when the embryo is

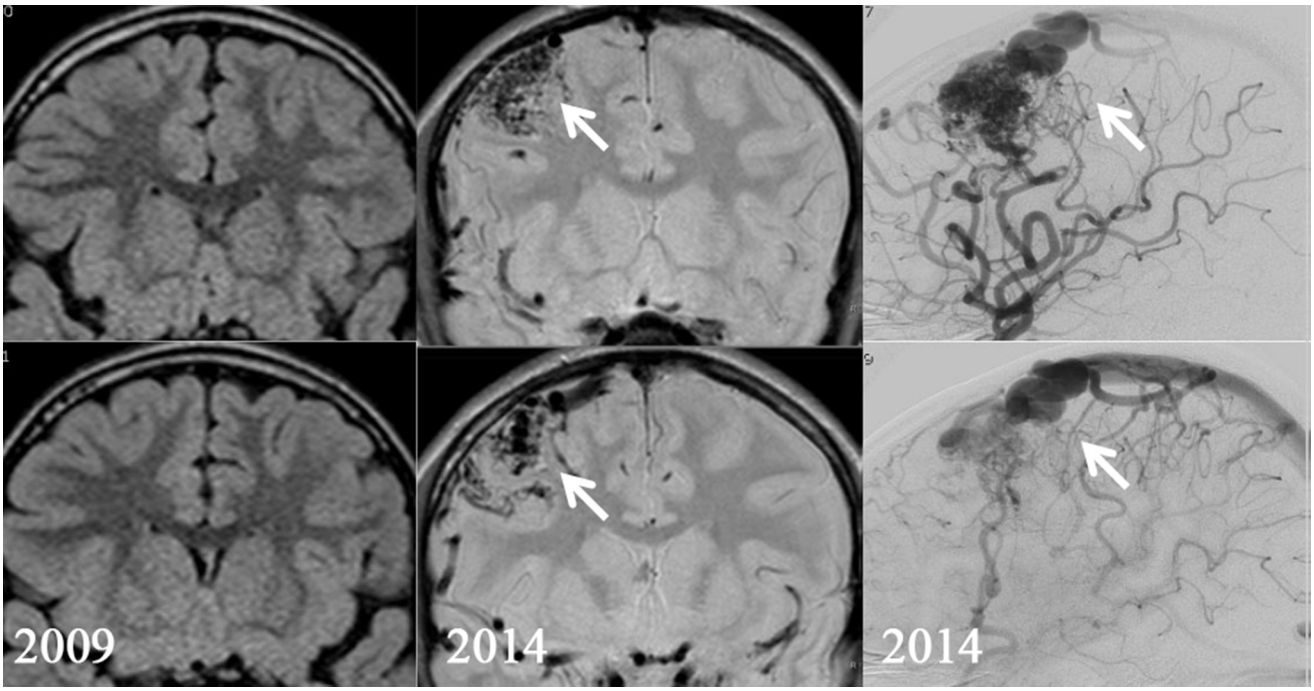

Figure 4. A 9-year-old girl underwent brain magnetic resonance imaging for questionable seizures. The findings of the initial study were unremarkable (2009). In 2014, 6 years later, she underwent repeat magnetic resonance imaging for headaches, which showed a de novo arteriovenous malformation formation (*arrows*).

between 40 and 80 mm long.[4] These investigators also stated that adult AVMs frequently incorporate evidence of an early failure in venous maturation.[4] Recently, Dalton et al.[15] after a meticulous MEDLINE search found 29 AVM cases of de novo formation. All patients had undergone negative high-resolution imaging at some point before the AVM diagnosis. High-resolution DSA was performed in 9 of 29 patients, finding no evidence or even suspicion of an AVM.[15] It is of interest that in all these reported cases, there was some prior external insult to the brain.[15] Moreover, several other anecdotal cases have shown similar results (**Figures 2–5**). According to the literature, de novo AVM formation seems to be the result of a previous cerebral insult such as brain tumor,[44,46,50] stroke,[42,60,64] trauma,[23,53] inflammation,[36,48] or other nonspecific disorders.[17,69] Thus, de novo AVM formation may represent a second hit with abnormal angiogenesis and vessel formation and sprouting.

Several investigators have reported AVM recurrence in the pediatric population, after previous complete excision of AVMs, confirmed by postoperative DSA.[19-22,24,76,77] However, it is unclear if this phenomenon could be a consequence of the relatively immature cerebral vasculature in children or because AVMs may not be congenital lesions. Thus, Karlsson et al.[25] believe that AVMs are developmental and not congenital malformations, which develop during brain maturation (i.e., until the age of 25 years). Similarly, Morgan et al.[78] stated that the likelihood of recurrence is greatest in childhood and in brain AVMs with deep venous drainage. On the other hand, in SIVMS (Scottish Intracranial Vascular Malformation Study), 2 cases were reported of spontaneous brain AVM obliteration 12 days and 2.4 years after presentation.[79]

In 1997, Lasjuanias[16] concluded that cerebral AVM formation is the result of a congenital event, which although occult at birth, becomes morphologically detectable later in life. Thus, AVM development is the complication of biological dysfunction, involving the vascular remodeling process. Additional triggers, the so-called revealing triggers, are necessary for this dysfunction to be shown. The target is likely to be located on the venous side of the capillaries.[16]

Implications of AVM Genetics

The genetic nature of cerebral AVMs remains controversial. Several gene studies have suggested that common genetic variations are associated with sporadic cerebral AVMs.[80-83] Leblanc et al.[84] reported that most of the genes and genetic risk factors associated with vascular malformations of the brain, including AVMs, have shown roles in vasculogenesis, angiogenesis, and vascular remodeling. Single nucleotide polymorphisms have been associated with a susceptibility to develop AVMs as well as with their progression to hemorrhage.[85] Genes involved in angiogenesis and inflammation may play a role in the pathophysiology of these lesions.[85] AVMs consist of active angiogenic and inflammatory dynamic lesions rather than a static congenital anomaly.[86] Several investigators[86,87] have reported overexpression of vascular endothelial growth factor, matrix metalloproteinase 9, interleukin 6, and transforming growth

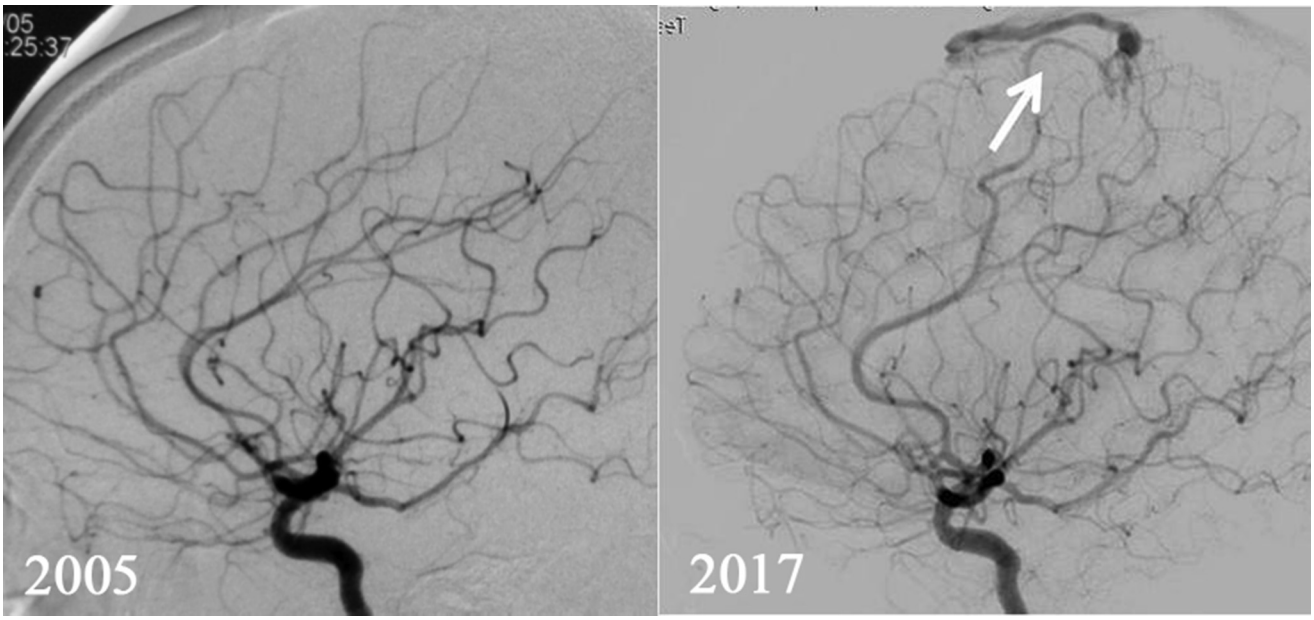

Figure 5. Control digital subtraction angiography images of a female patient harboring an already known left middle cerebral artery dysplasia. In 2017, a de novo arteriovenous malformation formation identified (*arrow*), which was not present on the obtained imaging workup in 2005. (With the permission of Dr. Emilio Lozupone.)

factor β in patients with AVM. Recent findings also suggest that angiogenic and inflammatory pathways synergize with underlying defects or hemodynamic derangements imposed on a congenital lesion injury to result in the clinical phenotype, perhaps in conjunction with as yet undetermined genetic or environmental influences.[88] Kim et al.[87] proposed a "response-to-injury" model of brain AVM pathogenesis.

Recent studies, incorporating many patients harboring AVMs and referring to their natural history, have focused on the estimation of the overall AVM hemorrhage rate and the annual risk of rupture and rerupture, as well as the identification of significant risk factors for bleeding.[89-93] However, none of these studies has evaluated whether cerebral AVMs are congenital or acquired lesions. This definition is of importance in understanding the biological behavior of AVMs but also for socioeconomic purposes, which may have an impact on the management and the overall outcome of these patients.

Limitations and Future Perspectives

There are limitations to our approach. First, de novo AVM cases are based mostly on case reports. Second, the exact pathophysiologic mechanisms of brain AVM formation remain obscure. There are theories, hypotheses, and proposed models, but the pathogenesis has yet to be elucidated. Large multicenter observational and genetic studies with long-term follow-up are necessary to determine the natural history of these rare, high-risk, vascular brain lesions. A prospective multidisciplinary international registry may also be helpful for addressing all these issues, by providing good-quality prospective data to researchers worldwide. One suggestion put forward is to investigate high-risk newborns (HHT) with screening brain magnetic resonance imaging studies to help elucidate the genetic nature or not of the familial brain AVMs. Issues associated with insurance cover for AVM treatment constitute a worldwide problem. In certain geographic areas (e.g., South America), most insurance companies provide no cover for AVM treatment based on their "congenital nature." The term "brain AV shunt of undetermined etiology" is frequently used in these circumstances to bypass this problem. Our consensus may provide further basis for cover of costs associated with brain AVM treatment.

CONCLUSIONS

AVMs are relatively rare, heterogeneous, and complex lesions, but they are the leading cause of hemorrhagic stroke in children and young adults and remain a significant risk of morbidity and mortality throughout the life of adults, despite significant improvements in their management and treatment. A better understanding of the natural history of these high-risk lesions is needed. Taking into consideration their rarity, the differences between familial and sporadic cases, their complex nature, and their challenging management, our consensus may help toward an agreement for approaching these patients harboring AVMs. An interaction between genetic susceptibility and environmentally acquired factors seems to be the most possible pathophysiologic mechanism of brain AVM formation. All participants believed that the presence of genetic variations alone is not enough for AVM formation and that a second hit is always required. Also, they all agreed that the congenital or otherwise character of intracranial AVMs may have no direct impact on their management, but it can

have considerable insurance implications and thus indirectly influence the patient's overall outcome.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Michael Söderman, and Dr. Emilio Lozupone. Author contributions to the study and manuscript preparation include the following: conception and design of the study, K.N.F. and A.T.; acquisition of data, all authors; analysis and interpretation of data, A.T. and C.T.; drafting the article, A.T. and K.N.F.; critically revising the article, K.N.F.; and reviewing final version of the manuscript and approving it for submission, all authors.

REFERENCES

1. Porter AJ, Bull J. Some aspects of the natural history of cerebral arteriovenous malformation. *Br J Radiol*. 1969;42:667-675.
2. Parkinson D, Bachers G. Arteriovenous malformations. Summary of 100 consecutive supratentorial cases. *J Neurosurg*. 1980;53:285-299.
3. Yasargil MG. *AVM of the Brain, History, Embryology, Pathological Considerations, Hemodynamics, Diagnostic Studies, Microsurgical Anatomy*. New York, NY: Thieme; 1987.
4. Mullan S, Mojtahedi S, Johnson DL, Macdonald RL. Embryological basis of some aspects of cerebral vascular fistulas and malformations. *J Neurosurg*. 1996;85:1-8.
5. Andaluz N, Myseros JS, Sathi S, Crone KR, Tew JM Jr. Recurrence of cerebral arteriovenous malformations in children: report of two cases and review of the literature. *Surg Neurol*. 2004;62:324-331.
6. Waltimo O. The change in size of intracranial arteriovenous malformations. *J Neurol Sci*. 1973;19:21-27.
7. Kadoya C, Momota Y, Ikegami Y, Urasaki E, Wada S, Yokota A. Central nervous system arteriovenous malformations with hereditary hemorrhagic telangiectasia: report of a family with three cases. *Surg Neurol*. 1994;42:234-239.
8. Leblanc R, Melanson D, Wilkinson RD. Hereditary neurocutaneous angiomatosis. Report of four cases. *J Neurosurg*. 1996;85:1135-1142.
9. Komiyama M. Pathogenesis of brain arteriovenous malformations. *Neurol Med Chir (Tokyo)*. 2016;56:317-325.
10. van Beijnum J, van der Worp HB, Schippers HM, et al. Familial occurrence of brain arteriovenous malformations: a systematic review. *J Neurol Neurosurg Psychiatry*. 2007;78:1213-1217.
11. Herzig R, Burval S, Vladyka V, et al. Familial occurrence of cerebral arteriovenous malformation in sisters: case report and review of the literature. *Eur J Neurol*. 2000;7:95-100.
12. Larsen PD, Hellbusch LC, Lefkowitz DM, Schaefer GB. Cerebral arteriovenous malformation in three successive generations. *Pediatr Neurol*. 1997;17:74-76.
13. Willinsky RA, Lasjaunias P, Terbrugge K, Burrows P. Multiple cerebral arteriovenous malformations (AVMs). Review of our experience from 203 patients with cerebral vascular lesions. *Neuroradiology*. 1990;32:207-210.
14. Delev D, Pavlova A, Grote A, et al. NOTCH4 gene polymorphisms as potential risk factors for brain arteriovenous malformation development and hemorrhagic presentation. *J Neurosurg*. 2017;126:1552-1559.
15. Dalton A, Dobson G, Prasad M, Mukerji N. De novo intracerebral arteriovenous malformations and a review of the theories of their formation. *Br J Neurosurg*. 2018;32:305-311.
16. Lasjaunias P. A revised concept of the congenital nature of cerebral arteriovenous malformations. *Interv Neuroradiol*. 1997;3:275-281.
17. Morales-Valero SF, Bortolotti C, Sturiale C, Lanzino G. Are parenchymal AVMs congenital lesions? *Neurosurg Focus*. 2014;37:E2.
18. Petridis AK, Fischer I, Cornelius JF, et al. Demographic distribution of hospital admissions for brain arteriovenous malformations in Germany-estimation of the natural course with the big-data approach. *Acta Neurochir (Wien)*. 2016;158:791-796.
19. Akimoto H, Komatsu K, Kubota Y. Symptomatic de novo arteriovenous malformation appearing 17 years after the resection of two other arteriovenous malformations in childhood: case report. *Neurosurgery*. 2003;52:228-232.
20. Gabriel EM, Sampson JH, Wilkins RH. Recurrence of a cerebral arteriovenous malformation after surgical excision. *Case report. J Neurosurg*. 1996;84:879-882.
21. Kader A, Goodrich JT, Sonstein WJ, Stein BM, Carmel PW, Michelsen WJ. Recurrent cerebral arteriovenous malformations after negative postoperative angiograms. *J Neurosurg*. 1996;85:14-18.
22. Lindqvist M, Karlsson B, Guo WY, Kihlström L, Lippitz B, Yamamoto M. Angiographic long-term follow-up data for arteriovenous malformations previously proven to be obliterated after gamma knife radiosurgery. *Neurosurgery*. 2000;46:803-810.
23. Gonzalez LF, Bristol RE, Porter RW, Spetzler RF. De novo presentation of an arteriovenous malformation. Case report and review of the literature. *J Neurosurg*. 2005;102:726-729.
24. O'Shaughnessy BA, Di Patri AJ Jr, Parkinson RJ, Batjer HH. Development of a de novo cerebral arteriovenous malformation in a child with sickle cell disease and moyamoya arteriopathy. Case report. *J Neurosurg*. 2005;102(2 suppl):238-243.
25. Karlsson B, Johansson AV, Yang HC, et al. A novel method to determine the natural course of unruptured brain arteriovenous malformations without the need for follow-up information. *J Neurosurg*. 2018;129(suppl 1):10-16.
26. Karlsson B, Lindquist C, Johansson A, Steiner L. Annual risk for the first hemorrhage from untreated cerebral arteriovenous malformations. *Minim Invasive Neurosurg*. 1997;40:40-46.
27. Brown RD Jr, Wiebers DO, Forbes G, et al. The natural history of unruptured intracranial arteriovenous malformations. *J Neurosurg*. 1988;68:352-357.
28. Crawford PM, West CR, Chadwick DW, Shaw MD. Arteriovenous malformations of the brain: natural history in unoperated patients. *J Neurol Neurosurg Psychiatry*. 1986;49:1-10.
29. Fults D, Kelly DL Jr. Natural history of arteriovenous malformations of the brain: a clinical study. *Neurosurgery*. 1984;15:658-662.
30. Graf CJ, Perret GE, Torner JC. Bleeding from cerebral arteriovenous malformations as part of their natural history. *J Neurosurg*. 1983;58:331-337.
31. Ogilvy CS, Stieg PE, Awad I, et al. Recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. *Circulation*. 2001;103:2644-2657.
32. Ondra SL, Troupp H, George ED, Schwab K. The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. *J Neurosurg*. 1990;73:387-391.
33. Achrol AS, Guzman R, Varga M, Adler JR, Steinberg GK, Chang SD. Pathogenesis and radiobiology of brain arteriovenous malformations: implications for risk stratification in natural history and posttreatment course. *Neurosurg Focus*. 2009;26:E9.
34. Alvarez H, Perry V, Solle M, Castillo M. De novo cerebral arteriovenous malformation in a child with previous cavernous malformation and developmental venous anomaly. *J Neurosurg Pediatr*. 2012;9:327-330.
35. Bai Y, He C, Zhang H, Ling F. De novo multiple dural arteriovenous fistulas and arteriovenous malformation after embolization of cerebral arteriovenous fistula: case report. *Childs Nerv Syst*. 2012;28:1981-1983.
36. Bulsara KR, Alexander MJ, Villavicencio AT, Graffagnino C. De novo cerebral arteriovenous malformation: case report. *Neurosurgery*. 2002;50:1137-1141.
37. Dogan SN, Bagcilar O, Mammadov T, Kizilkilic O, Islak C, Kocer N. De novo development of a cerebral arteriovenous malformation: case report and review of the literature. *World Neurosurg*. 2019;126:257-260.

38. Friedman JA, Pollock BE, Nichols DA. Development of a cerebral arteriovenous malformation in an adult documented by serial angiography. *J Neurosurg*. 2000;93:1058-1061.

39. Fujimura M, Kimura N, Ezura M, Niizuma K, Uenohara H, Tominaga T. Development of a de novo arteriovenous malformation after bilateral revascularization surgery in a child with moyamoya disease. *J Neurosurg Pediatr*. 2014;13:647-649.

40. Fuse T, Niwa Y, Umezu M, Yamada K. Growth of occult arteriovenous malformation after cerebral hemorrhage demonstrated by serial magnetic resonance imaging-case report. *Neurol Med Chir (Tokyo)*. 2001;41:83-86.

41. Harris OA, Chang SD, Harris BT, Adler JR. Acquired cerebral arteriovenous malformation induced by an anaplastic astrocytoma: an interesting case. *Neurol Res*. 2000;22:473-477.

42. Jeffree RL, Stoodley MA. Postnatal development of arteriovenous malformations. *Pediatr Neurosurg*. 2009;45:296-304.

43. Kilbourn KJ, Spiegel G, Killory BD, Kureshi I. Case report of a de novo brainstem arteriovenous malformation in an 18-year-old male and review of the literature. *Neurosurg Rev*. 2014;37:685-691.

44. Koch MJ, Agarwalla PK, Stapleton CJ, Ogilvy CS, Loeffler JS. De novo development of a cerebral arteriovenous malformation following radiation therapy: case report and an update to classical arteriovenous malformation nomenclature. *J Clin Neurosci*. 2016;28:162-167.

45. Krayenbühl HA. Angiographic contribution to the problem of enlargement of cerebral arteriovenous malformations. *Acta Neurochir (Wien)*. 1977;36:215-242.

46. Lo Presti A, Rogers JM, Assaad NNA, Rodriguez ML, Stoodley MA, Morgan MK. De novo brain arteriovenous malformation after tumor resection: case report and literature review. *Acta Neurochir (Wien)*. 2018;160:2191-2197.

47. Lv X, Wang G. Review of de novo cerebral arteriovenous malformation: haemorrhage risk, treatment approaches and outcomes. *Neuroradiol J*. 2018;31:224-229.

48. Mahajan A, Manchandia TC, Gould G, Bulsara KR. De novo arteriovenous malformations: case report and review of the literature. *Neurosurg Rev*. 2010;33:115-119.

49. Markham L, Hollingworth M. De novo arteriovenous malformation in a 4 year old boy with headache and no previous cerebrovascular disease. *J Neurol Neurosci*. 2015;6:36.

50. Mathon B, Blauwblomme T, Bolle S, et al. De novo arteriovenous malformation after brain radiotherapy for medulloblastoma in a child. *Neurology*. 2013;81:398-399.

51. McKinney JS, Steineke T, Nochlin D, Brisman JL. De novo formation of large arteriovenous shunting and a vascular nidus mimicking an arteriovenous malformation within an anaplastic oligodendroglioma: treatment with embolization and resection. *J Neurosurg*. 2008;109:1098-1102.

52. Mendelow AD, Erfurth A, Grossart K, Macpherson P. Do cerebral arteriovenous malformations increase in size? *J Neurol Neurosurg Psychiatry*. 1987;50:980-987.

53. Miller BA, Bass DI, Chern JJ. Development of a de novo arteriovenous malformation after severe traumatic brain injury. *J Neurosurg Pediatr*. 2014;14:418-420.

54. Miyasaka Y, Nakahara K, Takagi H, Hagiwara H. Development of multiple cerebral arteriovenous malformations documented in an adult by serial angiography. Case report. *J Neurosurg*. 2003;98:190-193.

55. Morioka T, Nishio S, Hikita T, Chung LH, Soejima T. Marked growth of an angiographically occult arteriovenous malformation: case report. *Neurosurgery*. 1988;23:101-103.

56. Nakamura M, Samii A, Lang JM, Gotz F, Samii M, Krauss JK. De novo AVM growth secondary to implantation of genetically modified allogeneic mesenchymal stem cells in the brain. *Neurosurgery*. 2016;78:E596-E600.

57. Neil JA, Li D, Stiefel MF, Hu YC. Symptomatic de novo arteriovenous malformation in an adult: case report and review of the literature. *Surg Neurol Int*. 2014;5:148.

58. Nussbaum ES, Heros RC, Madison MT, Awasthi D, Truwit CL. The pathogenesis of arteriovenous malformations: insights provided by a case of multiple arteriovenous malformations developing in relation to a developmental venous anomaly. *Neurosurgery*. 1998;43:347-352.

59. Ozsarac M, Aksay E, Kiyan S, Unek O, Gulec FF. De novo cerebral arteriovenous malformation: Pink Floyd's song "Brick in a wall" as warning sign. *J Emerg Med*. 2012;43:e17-e20.

60. Pabaney AH, Rammo RA, Tahir RA, Seyfried D. Development of de novo arteriovenous malformation following ischemic stroke: case report and review of current literature. *World Neurosurg*. 2016;96, 608.e5-608.e12.

61. Peeters FL. Angiographically demonstrated larger vascular malformation in a patient with a normal angiogram 23 years before. *Neuroradiology*. 1982;23:113-114.

62. Rodriguez Arias C, Martinez R, Rey G, Bravo G. Recurrence in a different location of a cerebral arteriovenous malformation in a child after radiosurgery. *Childs Nerv Syst*. 2000;16:363-365.

63. Santos R, Aguilar-Salinas P, Entwistle JJ, Aldana PR, Beier AD, Hanel RA. De novo arteriovenous malformation in a pediatric patient: case report and review of the literature. *World Neurosurg*. 2018;111:341-345.

64. Schmit BP, Burrows PE, Kuban K, Goumnerova L, Scottt RM. Acquired cerebral arteriovenous malformation in a child with moyamoya disease. *Case report. J Neurosurg*. 1996;84:677-680.

65. Shi S, Gupta R, Moore JM, et al. De novo AVM formation following venous sinus thrombosis and prior AVM resection in adults: report of 2 cases. *J Neurosurg*. 2018;128:506-510.

66. Shidoh S, Kobayashi M, Akaji K, Kano T, Tanizaki Y, Mihara B. De novo arteriovenous malformation after aneurysm clipping. *NMC Case Rep J*. 2017;4:89-92.

67. Shimoda Y, Osanai T, Nakayama N, et al. De novo arteriovenous malformation in a patient with hereditary hemorrhagic telangiectasia. *J Neurosurg Pediatr*. 2016;17:330-335.

68. Song JK, Niimi Y, Kupersmith MJ, Berenstein A. Postnatal growth and development of a cerebral arteriovenous malformation on serial magnetic resonance imaging in a child with hemangiomatosis. *J Neurosurg*. 2007;106(suppl 5):384-387.

69. Stevens J, Leach JL, Abruzzo T, Jones BV. De novo cerebral arteriovenous malformation: case report and literature review. *AJNR Am J Neuroradiol*. 2009;30:111-112.

70. Wu J, Li Y, Cao Y, Wang S. De novo cerebral arteriovenous malformations: is epileptic seizure a potential trigger? *Childs Nerv Syst*. 2014;30:1277-1281.

71. Yeo JJ, Low SY, Seow WT, Low DC. Pediatric de novo cerebral AVM: report of two cases and review of literature. *Childs Nerv Syst*. 2015;31:609-614.

72. Arteriovenous Malformation Study Group. Arteriovenous malformations of the brain in adults. *N Engl J Med*. 1999;340:1812-1818.

73. Di Rocco C, Tamburrini G. Sturge-Weber syndrome. *Childs Nerv Syst*. 2006;22:909-921.

74. Reck SD, Zacks DN, Eibschitz-Tsimhoni M. Retinal and intracranial arteriovenous malformations: Wyburn-Mason syndrome. *J Neuroophthalmol*. 2005;25:205-208.

75. Potter CA, Armstrong-Wells J, Fullerton HJ, et al. Neonatal giant pial arteriovenous malformation: genesis or rapid enlargement in the third trimester. *J Neurointerv Surg*. 2009;1:151-153.

76. Humphreys RP, Hoffman HJ, Drake JM, Rutka JT. Choices in the 1990s for the management of pediatric cerebral arteriovenous malformations. *Pediatr Neurosurg*. 1996;25:277-285.

77. Sonstein WJ, Kader A, Michelsen WJ, Llena JF, Hirano A, Casper D. Expression of vascular endothelial growth factor in pediatric and adult cerebral arteriovenous malformations: an immunocytochemical study. *J Neurosurg*. 1996;85:838-845.

78. Morgan MK, Patel N, Simons M, Ritson EA, Heller GZ. Influence of the combination of patient age and deep venous drainage on brain AVM recurrence after surgery: case series. *J Neurosurg*. 2012;117:934-941.

79. Al-Shahi Salman R, White PM, Counsell CE, et al. Outcome after conservative management or intervention for unruptured brain arteriovenous malformations. *JAMA*. 2014;311:1661-1669.

80. Pawlikowska L, Tran MN, Achrol AS, et al. Polymorphisms in transforming growth factor-B-related genes ALK1 and ENG are associated with sporadic brain arteriovenous malformations. *Stroke*. 2005;36:2278-2280.

81. Kim H, Hysi PG, Pawlikowska L, et al. Common variants in interleukin-1-beta gene are associated with intracranial hemorrhage and susceptibility to brain arteriovenous malformation. *Cerebrovasc Dis*. 2009;27:176-182.

82. Su H, Kim H, Pawlikowska L, et al. Reduced expression of integrin alphavbeta8 is associated with brain arteriovenous malformation pathogenesis. *Am J Pathol*. 2010;176:1018-1027.

83. Mikhak B, Weinsheimer S, Pawlikowska L, et al. Angiopoietin-like 4 (ANGPTL4) gene polymorphisms and risk of brain arteriovenous malformations. *Cerebrovasc Dis*. 2011;31:338-345.

84. Leblanc GG, Golanov E, Awad IA, Young WL. Biology of Vascular Malformations of the Brain NINDS Workshop Collaborators. Biology of vascular malformations of the brain. *Stroke*. 2009; 40:e694-e702.

85. Sturiale CL, Puca A, Sebastiani P, et al. Single nucleotide polymorphisms associated with sporadic brain arteriovenous malformations: where do we stand? *Brain*. 2013;136(pt 2):665-681.

86. Chen Y, Zhu W, Bollen AW, et al. Evidence for inflammatory cell involvement in brain arteriovenous malformations. *Neurosurgery*. 2008; 62:1340-1349.

87. Kim H, Su H, Weinsheimer S, Pawlikowska L, Young WL. Brain arteriovenous malformation pathogenesis: a response-to-injury paradigm. *Acta Neurochir Suppl*. 2011;111:83-92.

88. Kim H, Pawlikowska L, Chen Y, Su H, Yang GY, Young WL. Brain arteriovenous malformation biology relevant to hemorrhage and implication for therapeutic development. *Stroke*. 2009;40(3 suppl):S95-S97.

89. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: a meta-analysis. *J Neurosurg*. 2013;118:437-443.

90. Kim H, Al-Shahi Salman R, McCulloch CE, Stapf C, Young WL. MARS Coinvestigators. Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. *Neurology*. 2014;83:590-597.

91. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. *Stroke*. 2009;40:100-105.

92. Hernesniemi J, Dashti R, Juvela S, Vaart K, Niemela M, Laakso A. Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. *Neurosurgery*. 2008;63:823-831.

93. Morgan MK, Davidson AS, Assaad NNA, Stoodley MA. Critical review of brain AVM surgery, surgical results and natural history in 2017. *Acta Neurochir (Wien)*. 2017;159:1457-1478.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 5 July 2019; accepted 1 November 2019

Citation: World Neurosurg. (2020) 134:e799-e807.
https://doi.org/10.1016/j.wneu.2019.11.001

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***

1878-8750/$ - see front matter