Benefits of Treating Arteriovenous Malformations in Hereditary Hemorrhagic Telangiectasia: A Retrospective Analysis of 14 Patients

M. Neil Woodall, Peter Nakaji, Robert F. Spetzler

BACKGROUND: **Arteriovenous malformations (AVMs) are a cardinal feature of hereditary hemorrhagic telangiectasia (HHT). However, whether to treat brain AVMs in patients with HHT remains questionable because of the possible risks.**

METHODS: **We performed a retrospective study of patients with HHT who had been treated for brain AVMs at our institution from January 1, 2003, to December 31, 2016. An institutional database was queried for the phrases "hereditary hemorrhagic telangiectasia" and "HHT," and those patients who had been treated during the study period were identified. Data were extracted regarding presentation, AVM characteristics, treatment modality, and treatment outcomes.**

RESULTS: **We identified 14 patients (10 males, 4 females) with HHT who had had AVMs ($n = 27$) from the institutional database. The mean age of the patients was 43 years (range, 2–64). Of the 27 brain AVMs, 13 were Spetzler-Martin grade I, 12 were grade II, and 2 were grade III; none were grade IV or V. Treatment was by microsurgery only (11 AVMs in 10 patients), embolization followed by microsurgery (2 AVMs in 2 patients), and radiosurgery only (12 AVMs in 2 patients). AVM obliteration was achieved in 100% of the patients. No new fixed neurologic deficits developed after treatment of unruptured HHT AVMs.**

CONCLUSIONS: **The risk of treatment of brain AVMs in patients with HHT is quite low for appropriately selected patients with treatment individualized to radiosurgery, microsurgery, or a combination of embolization and microsurgery.**

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT; i.e., Osler-Weber-Rendu disease) is an autosomal dominant disorder characterized by epistaxis, mucocutaneous telangiectasia, and visceral arteriovenous malformations (AVMs).[1] HHT has an incidence of 25–400/1 million persons and affects ~60,000 U.S. patients.[2,3] The diagnosis is determined using the Curaçao criteria.[4] An HHT diagnosis is warranted when patients have ≥3 of the 4 cardinal features (i.e., recurrent epistaxis, mucocutaneous telangiectasias, visceral arteriovenous malformations, and a first-degree relative with HHT).[1] Complications include chronic anemia, the adverse effects of blood transfusions, hypoxemia (due to shunting through pulmonary AVMs), portal hypertension, and gastrointestinal bleeding.[2,5,6] The principal neurologic manifestations include ischemic stroke, brain abscess, and complications of AVMs involving the central nervous system.[7-9] The prevention of ischemic stroke and brain abscess is accomplished by an early diagnosis and treatment of pulmonary AVMs.[5] Prevention of hemorrhagic stroke due to rupture of a brain AVM is directed at early detection and treatment.[10] The optimal management of brain AVMs continues to be debated.[11,12]

Traditionally, brain AVMs in patients with HHT were treated in accordance with the treatment algorithms for sporadic brain AVMs.[13] Obliteration has generally been the goal, to reduce the risk of future rupture with the resultant neurologic morbidity and mortality.[14-16] However, recent reports have questioned this strategy.[11,12,17] Willemse et al.[12] argued that the natural history of brain AVMs in patients with HHT differs from that of sporadic AVMs, citing a rupture rate of 0.41%–0.72% and 2.2% per patient-year, respectively, for brain AVMs and sporadic AVMs in the ARUBA trial (a randomized trial of unruptured brain arteriovenous malformations). This seemingly low rupture rate in patients with HHT led Willemse et al.[12] to conclude that only patients with HHT with a negligible therapeutic risk profile should be treated. In 2016, Yang et al.[11] reported a rupture rate of 1.3% per patient-year for AVMs

Key words
- Arteriovenous malformation
- Embolization
- Hemorrhage
- Hereditary hemorrhagic telangiectasia
- Radiosurgery

Abbreviations and Acronyms
AVM: Arteriovenous malformation
HHT: Hereditary hemorrhagic telangiectasia

Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona, USA

To whom correspondence should be addressed: Robert F. Spetzler, M.D. [E-mail: Neuropub@barrowneuro.org]

Citation: World Neurosurg. X (2019) 3:100029. https://doi.org/10.1016/j.wnsx.2019.100029

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

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

Table 1. Types of Arteriovenous Malformations ($n = 27$) in 14 Patients with Hereditary Hemorrhagic Telangiectasia

AVM (*n*)	Spetzler-Martin Grade	Spetzler-Ponce Class
13	I	A
12	II	A
2	III	B
0	IV	C
0	V	C

AVM, arteriovenous malformation.

in patients with patients. In contrast, Gross and Du[16] had previously reported a rate of 2.2% per patient-year in their 2013 meta-analysis of cases of sporadic brain AVMs. Yang et al.[11] subsequently recommended conservative treatment because AVM multiplicity could increase the risk of treatment.

Before the appropriateness of treatment can be determined, the risks and benefits must be compared. Willemse et al.,[12] Yang et al.,[11] and others have attempted to define the natural history of brain AVMs in patients with HHT. However, data have been lacking regarding the treatment risks in the reported studies. Although some investigators have suggested that the risks of treatment are increased in patients with HHT because of the multiplicity of AVMs,[11] this claim has not been substantiated. Despite the multiplicity of brain AVMs in these patients, the lesions will tend to be of low grade and superficial, with a low risk.[11,12,18,19] Furthermore, previously reported natural history studies[11,12] were deeply flawed, leading to erroneous conclusions about the best treatment for these patients. Well-established treatment algorithms for sporadic brain AVMs have also been applied successfully for patients with HHT.[13] Thus, we hypothesized that the treatment risk for patients with HHT and brain AVMs would be quite low for appropriately selected patients undergoing individualized treatment.

METHODS

In the present retrospective study, we reviewed the records of patients with HHT who had undergone treatment for brain AVMs at our institution from 2003 to 2016. Using the terms "hereditary hemorrhagic telangiectasia" and "HHT," we searched the patients' medical history records, physical examination reports, and operative notes in the institutional database. The institutional review board approved the present study. The need for informed consent was waived owing to the retrospective nature of the research.

Data were extracted and tabulated on AVM size, location, Spetzler-Martin grade (I–V), Spetzler-Ponce class (A and B), history of rupture, treatment strategy, treatment outcomes, and preoperative and postoperative neurologic deficits. The patients who had undergone microsurgery or embolization plus microsurgery were evaluated using immediate postoperative catheter angiography to document AVM obliteration. The patients who had undergone stereotactic radiosurgery were followed up with annual serial magnetic resonance imaging studies for 3 years and catheter angiography to document obliteration. The data are reported as numbers (mean, median, and range) and percentages.

RESULTS

A total of 14 patients with HHT who had undergone treatment for 27 brain AVMs during the 14-year study period (January 1, 2003, to December 31, 2016) were included in the present study. Their median age was 43 years (range, 2–64). The median follow-up period was 38 months. Of the 14 patients, 10 were male and 4 were female. Nine patients had a solitary AVM, and 5 had multiple AVMs. Of the 27 brain AVMs, 13 were Spetzler-Martin grade I, 12 were grade II, and 2 were grade III (Table 1). No patient had a Spetzler-Martin grade IV or V lesion.

The 14 patients had undergone 18 treatments (i.e., ≥1 procedures directed at ≥1 AVMs). For instance, a patient who had had 1 Spetzler-Martin grade III AVM treated with Gamma Knife (Elekta AB, Stockholm, Sweden) stereotactic radiosurgery and microsurgery and 4 other Spetzler-Martin grade I AVMs treated with radiosurgery was considered to have had 2 treatments. A patient who had had 5 Spetzler-Martin grade I AVMs treated with radiosurgery was considered to have had 1 treatment. Five patients had multiple lesions. Of these 5 patients, 1 had received 1 Gamma Knife treatment for 5 Spetzler-Martin grade I AVMs. Two patients were treated with 2 microsurgical treatments for 2 separate AVMs. Two patients were treated with microsurgery for a ruptured AVM, followed by Gamma Knife radiosurgery for multiple small AVMs.

Table 2. Treatment Modalities*

Treatment Modality	AVMs ($n = 25$)†	Treatment ($n = 16$)‡	AVM Description
Microsurgery	11 (44)	11 (69)	Solitary, noneloquent
Embolization plus microsurgery	2 (8)	2 (13)	Adjacent to eloquent cortex ($n = 1$); high-flow fistulous component ($n = 1$)
Gamma Knife radiosurgery	12 (48)	3 (19)	Small and multiple

Data presented as *n* (%).
AVMs, arteriovenous malformations.
*Ten patients with 11 AVMs had undergone 11 microsurgery procedures; 2 patients with 2 AVMs had undergone 2 embolization procedures, followed by microsurgery; 2 patients with 12 AVMs had undergone 3 radiosurgery procedures.
†Spetzler-Ponce class A (Spetzler-Martin grades I and II).
‡Percentages sum to >100% because of rounding.

Table 3. Comparison of Reported Hereditary Hemorrhagic Telangiectasia Arteriovenous Malformations and Sporadic Arteriovenous Malformations Stratified by Spetzler-Ponce Class and Spetzler-Martin Grade

	HHT AVMs			Sporadic AVMs
Class (Grade)	Willemse et al.[12] (n = 28 AVMs in 24 Patients)*	Yang et al.[11] (n = 23 AVMs in 12 Patients)	Bharatha et al.[18] (n = 64 AVMs in 56 Patients)†	Bharatha et al.[18] (n = 1625 AVMs in 1933 Patients)
Spetzler-Ponce class A (Spetzler-Martin grade I and II)	24 (86)	18 (78)	52 (81)	736 (45)
Spetzler-Ponce class B (Spetzler-Martin grade III)	3 (11)	3 (13)	8 (13)	538 (33)
Spetzler-Ponce class C (Spetzler-Martin grade IV and V)	1 (4)	2 (9)	4 (6)	351 (22)

Data presented as n (%).
HHT, hereditary hemorrhagic telangiectasia; AVMs, arteriovenous malformations.
*Percentages sum to >100% because of rounding.
†Percentages sum to <100% because of rounding.

Of the 27 AVMs, 25 were Spetzler-Ponce class A and were treated in 16 treatments in the 14 patients. All 14 patients had ≥1 Spetzler-Ponce class A AVM. For the Spetzler-Ponce class A group (n = 25 AVMs with Spetzler-Martin grade I or II), 11 microsurgical treatments were directed at 11 Spetzler-Ponce class A AVMs in 10 patients (Table 2). Embolization, followed by microsurgery, was used to treat 2 AVMs in 2 patients: 1 lesion adjacent to eloquent cortex and 1 lesion with a high-flow fistulous component treated with preoperative embolization. Three Gamma Knife radiosurgery procedures were used to treat 12 AVMs (small and multiple) in 2 patients. Of the 2 Spetzler-Ponce class B AVMs (both Spetzler-Martin grade III), 1 was treated with microsurgery alone, and 1 was treated with microsurgery plus radiosurgery.

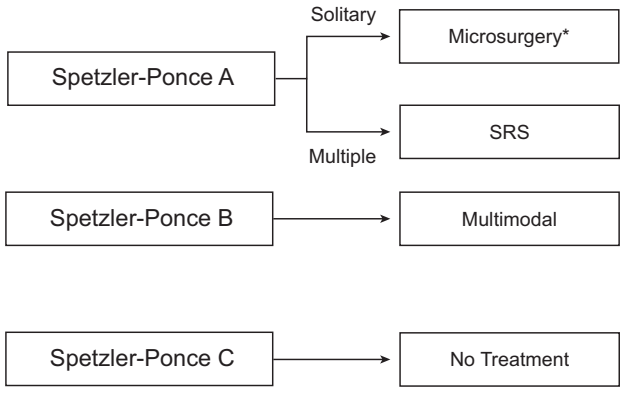

Figure 1. Flow chart illustrating the general treatment algorithm for patients with hereditary hemorrhagic telangiectasia (HHT) and brain arteriovenous malformations (AVMs). The treatment paradigm mirrors that for sporadic AVMs, with the exception of patients with multiple Spetzler-Ponce class A AVMs. AVM multiplicity is common in those with HHT but uncommon in the general non-HHT population. Spetzler-Ponce class C AVMs are quite rare in the HHT population, and none were in the present series. *Two patients with solitary Spetzler-Ponce class A AVMs were treated with multimodal therapy in the present series—1 with an AVM adjacent to eloquent cortex and 1 with a high-flow fistulous component. Treatment decisions must be on an individualized basis. SRS, stereotactic radiosurgery. (Used with permission from Barrow Neurological Institute, Phoenix, Arizona.)

Three patients presented with AVM hemorrhage and subsequent neurologic deficits (2 with hemiparesis and 1 with gait disturbance or ataxia). No permanent neurologic deficits resulted from treatment in the 14 patients with HHT. Transient (4+ of 5) upper extremity monoparesis that had developed in 1 patient after treatment of a small AVM in the primary sensory cortex had completely resolved at the first follow-up visit. No major treatment-related complications or deaths occurred. AVM obliteration (100%) was documented by cerebral angiography in all 14 patients. No new fixed neurologic deficits occurred after treatment.

DISCUSSION

Several investigators have questioned the appropriateness of treatment for brain AVMs in patients with HHT. Willemse et al.[12] proposed that the natural history of these AVMs is significantly more favorable than that of sporadic AVMs (rupture rate, 0.41%–0.72% vs. 2.2% per patient-year, respectively).[12,17] In addition, Yang et al.[11] reported a 1.3% per patient-year rupture rate in their series of patients with HHT. Both groups concluded that AVMs should be treated only in patients with HHT with an exceedingly low treatment risk. Yang et al.[11] suggested that AVM multiplicity increases the treatment risk.

However, these studies were subject to considerable bias warranting discussion. The risk of AVM rupture has generally been calculated as the number of AVM hemorrhages per number of patient-years. Most AVM natural history studies have calculated the patient-years by the duration between the date of AVM diagnosis and the date of rupture.[14-16] However, Willemse et al.[12] calculated patient-years by the duration between the time of birth and the date of rupture. Clearly, a method that uses the time of birth as the starting point will necessarily decrease the "risk of hemorrhage" by artificially increasing the number of patient-years.

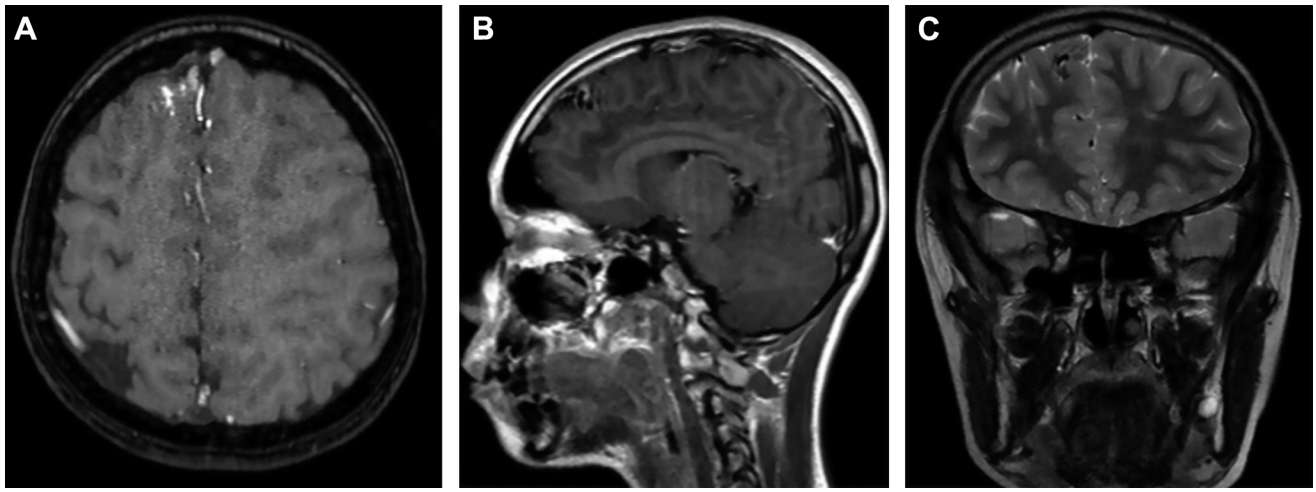

Figure 2. Preoperative (**A**) axial, (**B**) sagittal, and (**C**) coronal magnetic resonance images of a 10-year-old girl with hereditary hemorrhagic telangiectasia and a de novo right-sided frontal Spetzler-Martin grade I arteriovenous malformation. She was treated successfully with microsurgical resection. Right-sided parietal encephalomalacia was the result of a previous rupture of a separate right-sided parietal arteriovenous malformation treated at another institution. (Used with permission from Barrow Neurological Institute, Phoenix, Arizona.)

This method creates an "apples-to-oranges" comparison between the HHT population in the study by Willemse et al.[12] and the population in previous sporadic AVM natural history studies. Evidence has also suggested that AVMs in patients with HHT occur de novo,[20] which disputes the assumption that they have necessarily been present at birth. Therefore, the method of Willemse et al.[12] likely underestimated the rupture rates for AVMs in patients with HHT.

Yang et al.[11] reviewed the cases of 531 patients with 542 AVMs treated at their institution, focusing specifically on 12 patients with HHT and 23 AVMs. For the patients with HHT, the rupture rate of 1.3% per patient-year was considerably less than the rupture rate of 2.2% per patient-year for the unruptured sporadic AVMs in the ARUBA trial.[17] These findings led Yang et al.[11] to recommend conservative management for patients with HHT and brain AVMs. Although their methods were uniform in comparing the rupture risk for HHT and sporadic AVMs, their findings might have been subject to a substantial lead-time bias. The current HHT guidelines recommend routine screening of the brain with magnetic resonance imaging to identify AVMs,[1] and brain AVMs have often been discovered by screening. Yang et al.[11] found that 7 of 12 patients with HHT had a non-neurologic presentation, which resulted in a mean observation period of 12.5 years for those with AVMs compared with 2.7 years for patients with sporadic AVMs. The mean age was 23.3 years in the HHT group and 36.8 years in the sporadic group. These findings suggest that screening patients with HHT resulted in earlier diagnosis and longer observation periods, which artificially lowered the results of the rupture risk calculations. During the follow-up period, 1 patient had presented with hemorrhage and 1 patient had presented with 2 hemorrhages. Despite advocating for conservative management of HHT AVMs, Yang et al.[11] had 2 patients in their series with Spetzler-Martin grade I AVMs who had good outcomes after microsurgery.

Bharatha et al.[18] summarized the features of AVMs in a large multicenter cohort of patients with HHT. A key finding was that AVM multiplicity predicted for the HHT diagnosis. Patients with multiple brain AVMs were 86 times more likely to have HHT than were patients with 1 AVM. Thus, some investigators have argued that treatment risk is increased in patients with HHT owing to AVM multiplicity.[11] To date, no reported data have suggested that AVM treatment in the setting of HHT is more dangerous than the treatment of sporadic AVMs. In contrast, patients with HHT and AVMs might actually have a more favorable risk profile than patients with sporadic AVMs.

The AVMs in patients with HHT tend to be small (<3 cm in 88%–100%) and cortically located (85%–90%) and to have superficial venous drainage (75%).[18,19] Thus, HHT AVMs tend to be low grade. In the study by Bharatha et al.,[18] 81% were Spetzler-Martin grade I or II (Spetzler-Ponce class A). This finding contrasts starkly with the rate of 45% for sporadic AVMs that were Spetzler-Martin grade I or II (Spetzler-Ponce class A; **Table 3**).[11,12,18] Treatment of low-grade AVMs has long been associated with a lower treatment risk and improved treatment efficacy. Surgical series dating back to the 1980s have shown a rate of neurologic deficit of <5% and a mortality rate of 0% for patients with Spetzler-Martin grade I and II lesions.[21] In 2016, Schramm et al.[22] reported a series of patients treated with microsurgery for Spetzler-Martin grade I or II lesions with a 100% obliteration rate, a 3.2% rate of neurologic deficit, and no deaths. The risk profile for radiosurgery has been similarly low for small lesions. AVM volumes of <1 mL have been associated with 100% obliteration rates after Gamma Knife radiosurgery compared with an 85% obliteration rate for AVMs 1–4 mL and a 58% obliteration rate for AVMs >4 mL.[23] The risks associated with stereotactic radiosurgery will also be lessened by the small lesion volume. As the lesion volume increases, the risk of symptomatic radiation necrosis will increase concomitantly.

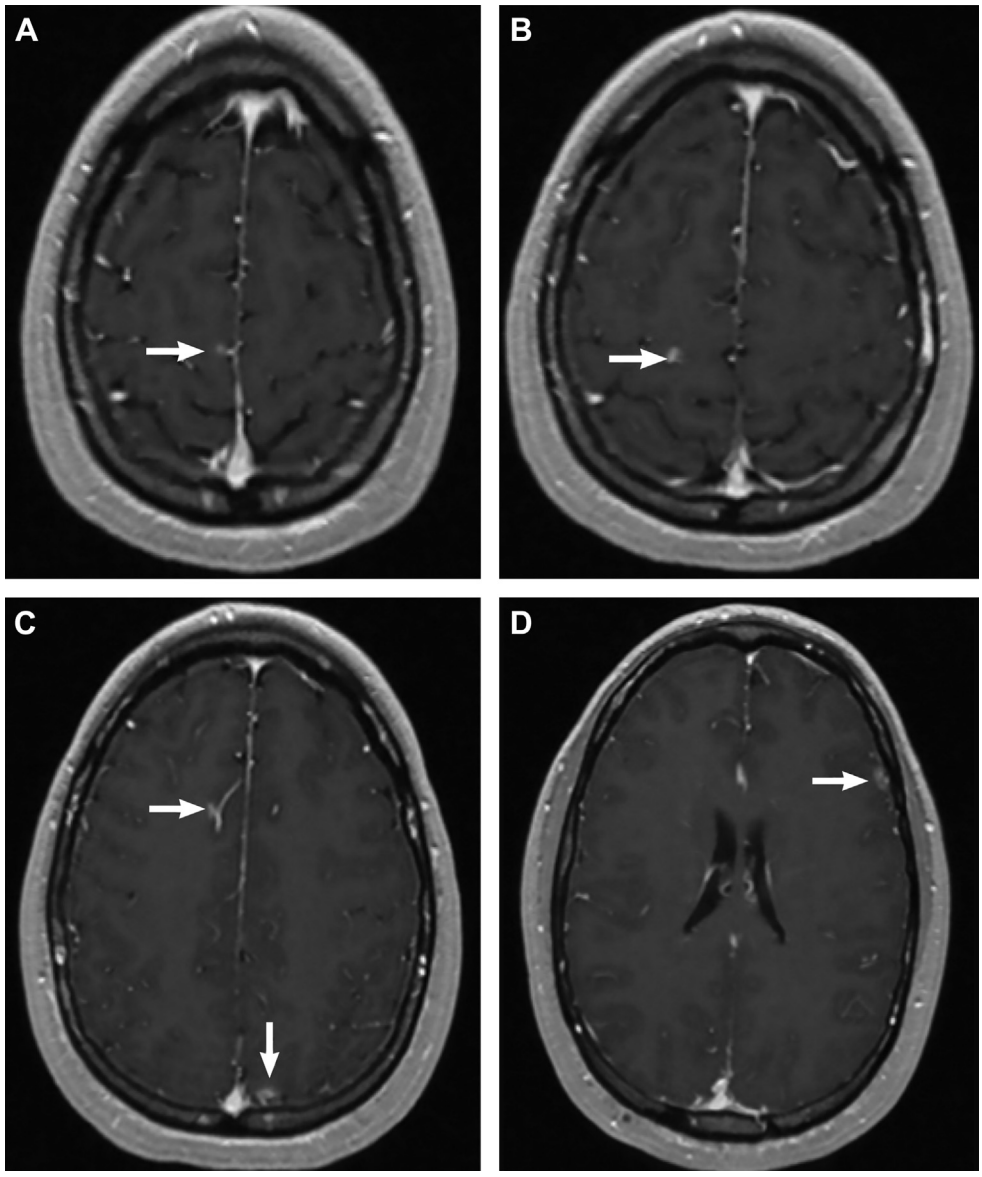

Figure 3. (**A**–**D**) Preoperative axial T1-weighted, contrast-enhanced magnetic resonance images of a 39-year-old man with hereditary hemorrhagic telangiectasia and multiple small arteriovenous malformations (*arrows*). The arteriovenous malformations were treated successfully using Gamma Knife radiosurgery. (Used with permission from Barrow Neurological Institute, Phoenix, Arizona.)

For instance, a 1-cm AVM lesion in the temporal lobe has a 0.59% chance of symptomatic radiation necrosis after Gamma Knife treatment. However, for a 4-cm lesion, the risk approaches 17%.[23]

A recent retrospective study that analyzed the data from patients with HHT from the brain HHT consortium found that the patients with HHT treated surgically for their AVMs had functional outcomes similar to those treated nonsurgically.[24] The investigators had compared patients with HHT who had undergone microsurgical resection of their AVMs with a group who had received nonsurgical therapy or observation. They found that the surgical group had fewer unfavorable outcomes.[24] Gamboa et al.[25] reported a large series of 39 patients with HHT and brain AVMs. They confirmed that most patients with HHT can be treated with single modality therapy—68% of patients in their series had received surgery (51%), embolization (6%), or stereotactic radiosurgery (11%) as stand-alone therapy. This finding likely reflected the low grade of brain AVMs in patients with HHT (96% were Spetzler-Ponce class A in the study by Gamboa et al.[25]).

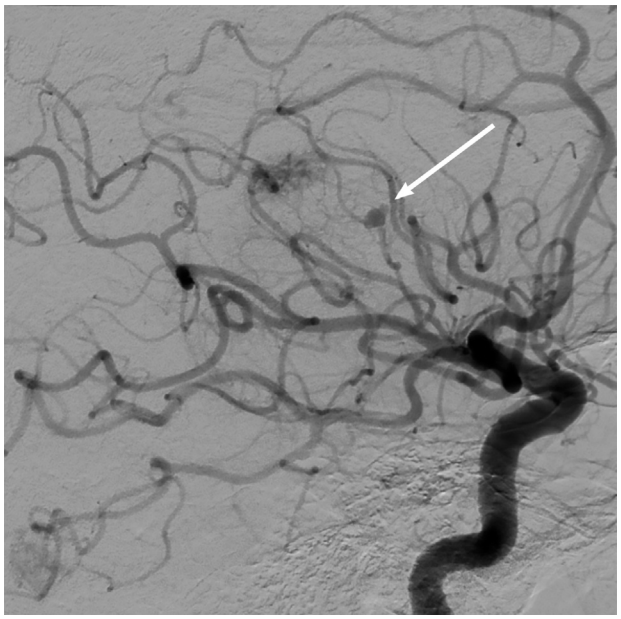

Figure 4. Lateral cerebral angiogram with right-sided internal carotid artery injection, magnified view demonstrating a Spetzler-Martin grade III arteriovenous malformation with a prenidal aneurysm (*arrow*) in a patient with hereditary hemorrhagic telangiectasia who had presented with right-sided basal ganglia hemorrhage and dense hemiparesis. (Used with permission from Barrow Neurological Institute, Phoenix, Arizona.)

As these findings suggest, good reasons exist for believing that HHT AVMs carry a favorable therapeutic risk profile. Our patients had a 100% AVM obliteration rate with no permanent neurologic deficits. One patient with a small AVM in the primary sensory cortex had experienced transient (4+ of 5) monoparesis that had completely resolved by the first follow-up examination. None of our patients died, no major surgical complications occurred, and no cases of symptomatic radiation necrosis developed. These excellent outcomes were due largely to the favorable characteristics of the lesions; 25 of 27 AVMs (93%) were Spetzler-Martin grade I or II lesions (i.e., Spetzler-Ponce class A; **Table 1**). Three patients with HHT (21%) had presented with AVM rupture. These ruptures had caused significant neurologic morbidity: 2 patients had significant hemiparesis and 1 had continued to have gait issues secondary to cerebellar dysfunction at the last follow-up evaluation. Kim et al.[26] recently showed that unruptured HHT AVMs carry a rupture risk of ~0.43% annually; however, previously ruptured HHT AVMs have a rupture risk of 10% annually. They recognized that a lead-time bias likely causes an underestimation of the rupture risk for patients with HHT and unruptured brain AVMs.[26] They were the first to show an increased risk of subsequent hemorrhage for previously ruptured AVMs in patients with HHT.[26] These findings support the notion that the natural history of HHT AVMs mirrors that of sporadic AVMs.[26]

Treatment algorithms have been proposed for sporadic AVMs that suggest microsurgery alone for Spetzler-Ponce class A lesions (Spetzler-Martin grade I or II), multimodality treatment for class B lesions (grade III), and no treatment for class C lesions (Spetzler-Martin grade IV or V) lesions (except for select cases).[13,27] We believe that these treatment algorithms can also be applied to patients with HHT. In the present 14-patient series, 11 class A AVMs in 10 patients (79%) were treated with microsurgery alone. Two class A AVMs in 2 patients (14%) were treated with embolization plus microsurgery: 1 small AVM adjacent to eloquent cortex and 1 AVM with a high-flow fistulous component. Twelve class A AVMs were treated in 2 patients (14%) with Gamma Knife radiosurgery. The 2 class B AVMs (grade III) in the present series were treated with multimodality therapy. In the present series, most AVMs were treated successfully with single-modality therapy, as in an earlier series.[19] The decision tree used for treating the patients in the present series according to the patients' Spetzler-Ponce classification is shown in **Figure 1**.

Case Example: Microsurgery

A 10-year-old girl with HHT presented with de novo formation of a right-sided frontal AVM found on surveillance imaging (**Figure 2**). Several years earlier, she had undergone successful microsurgical resection of a ruptured right parietal AVM. Because of her age, preoperative angiography was not performed to minimize her radiation exposure. A Spetzler-Martin grade I (Spetzler-Ponce class A) AVM was resected using standard microsurgical techniques. Immediate postoperative angiography demonstrated AVM obliteration.

Case Example: Radiosurgery

A 39-year-old man with HHT presented with multiple, small (<1 cm) AVMs found on brain magnetic resonance imaging (**Figure 3**). The multiplicity of lesions precluded microsurgical resection using a single approach. Thus, he underwent Gamma Knife stereotactic radiosurgery (18 Gy to the 50% isodose line). Follow-up angiography 3 years later demonstrated obliteration of the AVMs. In the traditional algorithms for sporadic AVM treatment, stereotactic radiosurgery has typically been reserved for surgically inaccessible lesions. Radiosurgery also can be used as a preoperative adjunct to microsurgical resection, with the deep or difficult portion of a high-grade AVM treated using radiosurgery, followed by resection of the superficial component subsequent to the radiation response. However, in patients with HHT, the presence of multiple small AVMs can indicate the need for stereotactic radiosurgery, a scenario seldom encountered in patients with sporadic AVMs.

Case Example: Multimodal Therapy

A 54-year-old man with a history of HHT had presented with headache and dense left-sided hemiparesis. A head computed tomography scan showed a right-sided basal ganglia hemorrhage with subependymal hyperdensity, suggestive of an AVM. Angiography revealed a Spetzler-Martin grade III AVM with a prenidal aneurysm (**Figure 4**). Endovascular embolization was attempted; however, the small lenticulostriate feeding artery could not be catheterized. The patient then underwent ligation of the feeding vessel that had resulted in the prenidal aneurysm, with intraoperative angiographic confirmation (i.e., the high-risk feature was treated using an open surgical approach [**Figure 5**]). The risk of definitive AVM resection was thought to outweigh the benefit, and the residual AVM was treated with Gamma Knife radiosurgery in a delayed fashion (16 Gy to the 50% isodose line) with good results.

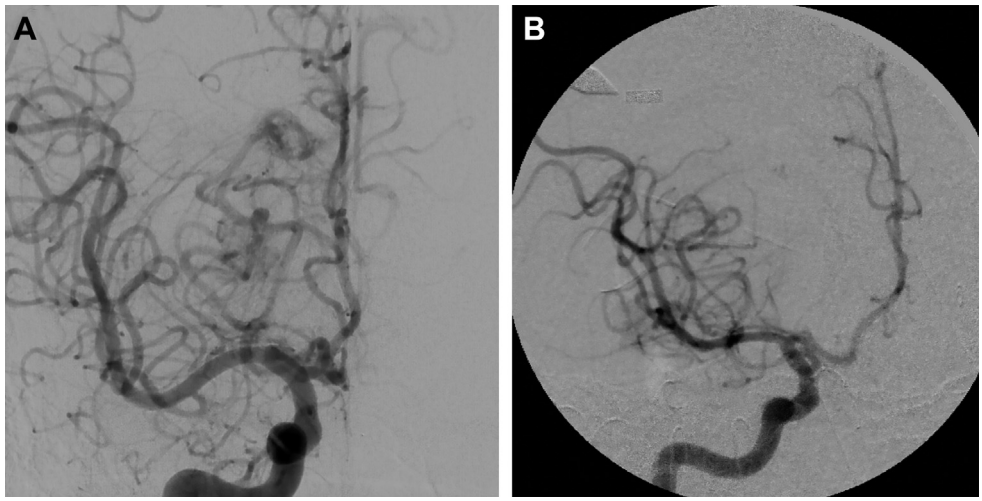

Figure 5. (**A**) Preoperative anteroposterior cerebral angiogram with right-sided internal carotid artery injection showing a Spetzler-Martin grade III arteriovenous malformation before ligation of the lenticulostriate feeding artery that had resulted in a prenidal aneurysm. (**B**) Postoperative oblique intraoperative cerebral angiogram with right-sided internal carotid artery injection after ligation of the lenticulostriate feeding artery and resultant elimination of the high-risk prenidal aneurysm. (Used with permission from Barrow Neurological Institute, Phoenix, Arizona.)

CONCLUSIONS

The present study represents a highly selected surgical series from a high-volume referral center; thus, the results might not be generalizable. The findings were subject to bias and the inherent limitations of a retrospective study. Our findings were also limited by the small number of patients ($n = 14$). However, few studies have focused on the issue of surgical risk for the treatment of AVMs in patients with HHT. Our findings support the idea that the appropriate selection of patients with HHT and brain AVMs can result in excellent outcomes. For the reasons we have outlined, we believe that the risk of rupture for AVMs in patients with HHT has been underestimated in the surgical data. Treatment must be individualized; however, these patients should be treated according to the well-established treatment algorithms proposed for the treatment of sporadic AVMs.[13,27] Several patients with HHT in the present series experienced neurologic morbidity as a result of untreated AVMs that had ruptured, which has been reported in other series.[28] Patients with HHT deserve the consideration of treatment of brain AVMs because hemorrhage can result in significant neurologic morbidity and death.[14-16]

The risk of rupture has been underestimated in the surgical data, primarily owing to the lead-time bias.[11,12,26] Some investigators have postulated that AVM multiplicity in patients with HHT increases the treatment risk; however, the data do not support this theory.[11] Brain AVMs in patients with HHT tend to be small and low grade and to have superficial venous drainage. These characteristics theoretically decrease the treatment risk and might increase the treatment efficacy.[11,12,18,19] In the present, small, highly selected surgical series, patients with HHT and AVMs had excellent treatment outcomes, with a 100% obliteration rate, no new permanent neurologic deficits, no major treatment-related complications, and no deaths. The goal of AVM management for patients with HHT should be the prevention of neurologic morbidity secondary to rupture. Each patient must be evaluated individually; however, we believe that the management of AVMs in patients with HHT should generally be approached using the well-established treatment algorithms used for the treatment of patients with sporadic AVMs.[13,27]

ACKNOWLEDGMENTS

The authors thank the staff of Neuroscience Publications at Barrow Neurological Institute for assistance with manuscript preparation.

REFERENCES

1. Faughnan ME, Palda VA, Garcia-Tsao G, et al, Group HHT Foundation International — Guidelines Working Group. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. *J Med Genet*. 2011;48:73-87.

2. Haitjema T, Westermann CJ, Overtoom TT, et al. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease): new insights in pathogenesis, complications, and treatment. *Arch Intern Med*. 1996;156:714-719.

3. Begbie ME, Wallace GM, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. *Postgrad Med J*. 2003;79:18-24.

4. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet*. 2000;91:66-67.

5. Gossage JR, Kanj G. Pulmonary arteriovenous malformations: a state of the art review. *Am J Respir Crit Care Med*. 1998;158:643-661.

6. Shovlin CL. Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment. *Blood Rev*. 2010;24:203-219.

7. Sobel D, Norman D. CNS manifestations of hereditary hemorrhagic telangiectasia. *AJNR Am J Neuroradiol*. 1984;5:569-573.

8. Sell B, Evans J, Horn D. Brain abscess and hereditary hemorrhagic telangiectasia. *South Med J*. 2008;101:618-625.

9. McDonald MJ, Brophy BP, Kneebone C. Rendu-Osler-Weber syndrome: a current perspective on cerebral manifestations. *J Clin Neurosci*. 1998;5:345-350.

10. Mandzia J, Henderson K, Faughnan M, White R Jr. Compelling reasons to screen brain in HHT. *Stroke*. 2001;32:2957-2958.

11. Yang W, Liu A, Hung AL, et al. Lower risk of intracranial arteriovenous malformation hemorrhage in patients with hereditary hemorrhagic telangiectasia. *Neurosurgery*. 2016;78:684-693.

12. Willemse RB, Mager JJ, Westermann CJ, Overtoom TT, Mauser H, Wolbers JG. Bleeding risk of cerebrovascular malformations in hereditary hemorrhagic telangiectasia. *J Neurosurg*. 2000;92:779-784.

13. Spetzler RF, Ponce FA. A 3-tier classification of cerebral arteriovenous malformations: clinical article. *J Neurosurg*. 2011;114:842-849.

14. ApSimon HT, Reef H, Phadke RV, Popovic EA. A population-based study of brain arteriovenous malformation: long-term treatment outcomes. *Stroke*. 2002;33:2794-2800.

15. 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.

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

17. Mohr JP, Parides MK, Stapf C, et al, International ARUBA Investigators. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet*. 2014;383:614-621.

18. Bharatha A, Faughnan ME, Kim H, et al. Brain arteriovenous malformation multiplicity predicts the diagnosis of hereditary hemorrhagic telangiectasia: quantitative assessment. *Stroke*. 2012;43:72-78.

19. Woodall MN, McGettigan M, Figueroa R, Gossage JR, Alleyne CH Jr. Cerebral vascular malformations in hereditary hemorrhagic telangiectasia. *J Neurosurg*. 2014;120:87-92.

20. Du R, Hashimoto T, Tihan T, Young WL, Perry V, Lawton MT. Growth and regression of arteriovenous malformations in a patient with hereditary hemorrhagic telangiectasia: case report. *J Neurosurg*. 2007;106:470-477.

21. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65:476-483.

22. Schramm J, Schaller K, Esche J, Bostrom A. Microsurgery for cerebral arteriovenous malformations: subgroup outcomes in a consecutive series of 288 cases. *J Neurosurg*. 2017;126:1056-1063.

23. Lunsford LD, Niranjan A, Kondziolka D, Sirin S, Flickinger JC. Arteriovenous malformation radiosurgery: a twenty year perspective. *Clin Neurosurg*. 2008;55:108-119.

24. Meybodi AT, Kim H, Nelson J, et al. Brain Vascular Malformation Consortium HHT Investigator Group. Surgical treatment vs nonsurgical treatment for brain arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia: a retrospective multicenter consortium study. *Neurosurgery*. 2018;82:35-47.

25. Gamboa NT, Joyce EJ, Eli I, et al. Clinical presentation and treatment paradigms of brain arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. *J Clin Neurosci*. 2018;51:22-28.

26. Kim H, Nelson J, Krings T, et al. Brain Vascular Malformation Consortium HHT Investigator Group. Hemorrhage rates from brain arteriovenous malformation in patients with hereditary hemorrhagic telangiectasia. *Stroke*. 2015;46:1362-1364.

27. Russin J, Cohen-Gadol AA. Editorial: what did we learn from the ARUBA trial? *Neurosurg Focus*. 2014;37:E9.

28. Kuo YH, Santoreneos S, Roos D, Brophy BP. Treatment of multiple arteriovenous malformations in pediatric patients with hereditary hemorrhagic telangiectasia and spontaneous hemorrhage: report of two cases. *J Neurosurg*. 2007;107(suppl):489-494.

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 14 November 2018; accepted 15 February 2019

Citation: World Neurosurg. X (2019) 3:100029. https://doi.org/10.1016/j.wnsx.2019.100029

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

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