New aneurysm formation and regrowth associated with rebleeding of residual pediatric ruptured arteriovenous malformation: patient series

Yoshihisa Matsumoto, MD, PhD,1 Yui Nagata, MD,1 Setsuko Nakagawa, MD, PhD,1 Takuro Hashikawa, MD,1 Hideki Sakai, MD,1 Shinji Takahashi, MD,1 Yosuke Hashimoto, MD,1 Shin Goto, MD,2 Yasuo Sugita, MD, PhD,1 and Kenji Takahashi, MD1

1Department of Neurosurgery, St. Mary's Hospital, Fukuoka, Japan; and2Department of Neurosurgery, Tanushimaru Central Hospital, Fukuoka, Japan

BACKGROUND If complete obliteration of ruptured pediatric arteriovenous malformation (AVM) cannot be achieved, the appropriate follow-up duration and predictors of rebleeding remain unknown.

OBSERVATIONS Pediatric patients with ruptured AVMs admitted to the authors' hospital within the past 30 years were evaluated. Rebleeding was confirmed in two patients. The first patient was a 5-year-old boy who experienced right thalamic hemorrhage. AVM was found in the bilateral thalamus and treated with stereotactic radiosurgery (SRS). New aneurysm formation and residual AVM regrowth were confirmed 21 years after the SRS. Eight months later, rebleeding occurred. The second patient was a 5-year-old boy who underwent removal of a left cerebellar hemorrhage and AVM. The residual AVM was treated with SRS. Residual AVM regrowth was detected at 6 years 7 months after SRS. Five months later, new aneurysm formation was confirmed. Two additional days later, rebleeding occurred.

LESSONS New aneurysm formation and residual AVM regrowth may predict rebleeding and can occur >20 years after the initial rupture and treatment. If AVM obliteration is not achieved, long-term follow-up is needed, even in adulthood, with attention to new aneurysm formation and residual AVM regrowth. Further treatment is recommended if these findings are confirmed.

https://thejns.org/doi/abs/10.3171/CASE22205

KEYWORDS arteriovenous malformation; pediatric; new aneurysm formation; regrowth; rebleeding

Hemorrhagic stroke accounts for half of all pediatric stroke cases.1 Arteriovenous malformation (AVM) is a common cause of symptomatic intracerebral hemorrhage (ICH).1,2 Rebleeding of pediatric ruptured AVM can induce functional deficits or death. Therefore, the main goal of treatment is to preserve neurological function by preventing secondary ICH.3 Although microsurgical removal, complete embolization, or combined treatment may provide an immediate and safe cure for AVM with low Spetzler-Martin (SM) grade,4 completely safe treatment is not always achieved.4 If treatment risk is high, observation is warranted despite confirmation of the residual AVM.

Even after achieving complete AVM obliteration, AVM recurrence is frequently reported in pediatric patients.5–7 Therefore, to detect persistent or recurrent AVM, repeat angiographic examinations up to 18 years of age are suggested.6 However, if complete AVM obliteration cannot be achieved, appropriate follow-up duration and predictors of rebleeding from the residual AVM remain unknown. The accurate predictors of impending rebleeding will allow us to consider the appropriate timing and types of additional treatments compared with their risks.

This study aimed to investigate the predictors of impending rebleeding in pediatric patients aged <18 years with ruptured AVMs admitted to our hospital within the past 30 years. Rebleeding occurred in two patients at 21 and 7 years after the initial rupture and treatment, respectively. In these patients, new aneurysm formation and residual AVM regrowth were confirmed before rebleeding occurred. Here, we report these two cases.

ABBREVIATIONS 3D = three-dimensional; AVM = arteriovenous malformation; CT = computed tomography; CTA = computed tomography angiography; DSA = digital subtraction angiography; ICH = intracerebral hemorrhage; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; SM = Spetzler-Martin; SRS = stereotactic radiosurgery.

INCLUDE WHEN CITING Published October 31, 2022; DOI: 10.3171/CASE22205.

SUBMITTED May 13, 2022. ACCEPTED September 9, 2022.

© 2022 The authors, CC BY-NC-ND 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/).
| Case No. | Age (yrs) | Sex | SM Grade | Initial Treatment | Residual AVM | Angiographic Outcome | Rebleeding | mRS Score | FU Duration |
|---------|-----------|-----|----------|------------------|-------------|---------------------|------------|-----------|-------------|
| 1       | 5         | M   | III      | Extraventricular drainage & SRS | +           | Regrowth w/ new AN formation | +          | 5         | 24 yrs, 1 mo |
| 2       | 5         | M   | III      | Op & SRS | +           | Regrowth w/ new AN formation | +          | 2         | 13 yrs, 1 mo |
| 3       | 10        | M   | III      | Op | +           | Regrowth w/o new AN formation | −          | 1         | 9 yrs, 10 mos |
| 4       | 15        | F   | IV       | Embolization for associated AN | +           | Residual AVM w/o change | −          | 1         | 4 yrs, 9 mos |
| 5       | 8         | F   | III      | SRS | +           | Size reduction of residual AVM | −          | 2         | 7 yrs, 9 mos |
| 6       | 11        | F   | II       | Embolization & SRS | +           | Size reduction of residual AVM | −          | 0         | 1 yr         |
| 7       | 13        | F   | IV       | Op & SRS | +           | Size reduction of residual AVM | −          | 1         | 26 yrs, 5 mos |
| 8       | 15        | F   | II       | Embolization & SRS | +           | Size reduction of residual AVM | −          | 1         | 12 yrs, 2 mos |
| 9       | 5         | F   | IV       | Hematoma evacuation & SRS | −           | Obliteration confirmed by MRI | −          | 2         | 10 yrs, 10 mos |
| 10      | 9         | M   | I        | Embolization & op & SRS | −           | Obliteration confirmed by DSA | −          | 1         | 2 yrs, 6 mos |
| 11      | 9         | F   | III      | Embolization, op & SRS | −           | Obliteration confirmed by DSA | −          | 1         | 5 yrs, 5 mos |
| 12      | 10        | F   | II       | Embolization & op & SRS | −           | Obliteration confirmed by DSA | −          | 1         | 1 yr, 7 mos |
| 13      | 10        | M   | III      | Embolization & op | −           | Obliteration confirmed by DSA | −          | 1         | 8 yrs, 3 mos |
| 14      | 11        | M   | III      | Embolization & op | −           | Obliteration confirmed by DSA | −          | 1         | 5 yrs, 5 mos |
| 15      | 11        | M   | II       | SRS | −           | Obliteration confirmed by DSA | −          | 1         | 7 yrs, 7 mos |
| 16      | 11        | M   | III      | Op | −           | Obliteration confirmed by MRI | −          | 1         | 7 yrs, 2 mos |
| 17      | 13        | M   | I        | Embolization & op | −           | Obliteration confirmed by DSA | −          | 0         | 2 yrs, 2 mos |
| 18      | 14        | M   | II       | Op | −           | Obliteration confirmed by DSA | −          | 1         | 5 yrs, 6 mos |
| 19      | 15        | F   | III      | Embolization & op | −           | Obliteration confirmed by DSA | −          | 1         | 4 yrs, 7 mos |
| 20      | 15        | F   | I        | Op | −           | Obliteration confirmed by DSA | −          | 1         | 1 yr, 10 mos |
| 21      | 16        | F   | II       | Embolization & op | −           | Obliteration confirmed by DSA | −          | 2         | 3 yrs, 11 mos |
| 22      | 17        | M   | II       | Op | −           | Obliteration confirmed by DSA | −          | 0         | 26 yrs, 4 mos |
| 23      | 17        | M   | II       | Op | −           | Obliteration confirmed by DSA | −          | 1         | 4 yrs, 4 mos |

AN = aneurysm; FU = follow-up; mRS = modified Rankin Scale.
Study Description
This study enrolled consecutive pediatric patients admitted to our hospital for ruptured AVMs between January 1, 1990, and December 31, 2019. The inclusion criterion was intracranial hemorrhage that occurred before 18 years of age. The final consultation date was defined as the final date of patient status confirmation. The minimum follow-up duration was 365 days.

During the study period, 27 pediatric patients (15 boys) with ruptured AVMs were admitted to our hospital. The average age at the time of initial hemorrhage was 11.7 ± 3 years. Among the 27 patients, 2 died in the intensive care unit during the initial admission due to intracranial hypertension despite extraventricular drainage and/or osmotherapy. The follow-up of two patients was discontinued in our hospital within 365 days because they were admitted to another hospital. Therefore, 23 patients were investigated in this study.

Recurrence of an AVM was defined as a new hemorrhage or new radiological evidence of an AVM in a patient whose examination with conventional angiography soon after treatment indicated complete AVM obliteration. Regrowth of an AVM was defined as an increase in the size of a residual AVM confirmed by angiography.

Treatments and Long-Term Outcomes
Regarding the initial treatment, six patients were treated with surgery alone, one with embolization alone, and two with stereotactic radiosurgery (SRS) alone. Fourteen patients were treated with combined treatment (Table 1).

The average age during the final outcome assessment was 20.1 ± 7 years, and the mean follow-up period was 6.7 years (range, 1–26 years). The clinical outcomes of the patients were as follows: Functional independence (modified Rankin Scale score, 0–2) was achieved in 22 patients. One patient had severe disability (modified Rankin Scale score, 5).

The obliteration of the AVM was confirmed by magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) and digital subtraction angiography (DSA) in 2 and 13 patients, respectively (Fig. 1). We did not encounter recurrence of the AVM.

Size reduction after SRS was observed in four patients, who remained under continuous observation.

One patient underwent target embolization of the associated aneurysm and observation due to high SM grade. The residual AVM of this patient has not grown in the past 4 years, and the patient remains under continuous observation.

In the other three patients, new aneurysm formation and/or regrowth of the residual AVM were observed. In one patient, a small residual diffuse AVM in the left cerebral region was identified on DSA after the initial surgery. The regrowth of the residual AVM was confirmed by DSA 9 years after the initial surgery. New aneurysm formation has not been confirmed. Endovascular embolization and repeat AVM removal were performed 7 months later. The remaining two patients (cases 1 and 2) experienced rebleeding.

Illustrative Cases
Rebleeding Case 1
A 5-year-old boy presented with coma. The patient was admitted to our hospital, and right thalamic hemorrhage with intraventricular hemorrhage was confirmed. The patient underwent extraventricular drainage. AVM was identified in the bilateral thalamus and treated with SRS. The patient had left hemiparesis; however, he was able to walk without assistance and to return home.

The surveillance MRI examination was performed 6 years after SRS at our institute, and the residual AVM was observed (Fig. 2). Subsequent follow-up examinations were conducted at another hospital. He was able to work 21 years after SRS. However, a new aneurysm formation at the residual AVM in the left thalamus and residual AVM regrowth were detected on surveillance imaging.

Eight months after the new aneurysm formation and residual AVM regrowth were detected, the patient was in a comatose state suddenly. The patient was transferred to our hospital, where rebleeding was confirmed. The hemorrhage spread from the left thalamus to the lateral ventricle and hematoma cavity in the right thalamus. The patient underwent extraventricular drainage and survived; however, his neurological status was bedridden. He was discharged to a long-term care hospital. His modified Rankin Scale score worsened from 1 to 5.

We requested past imaging from another hospital when the rebleeding was detected. We could confirm only the surveillance MRI/MRA examination performed 21 years after SRS. We were
unable to confirm the frequency and type of surveillance imaging performed there.

Rebleeding Case 2

A 5-year-old boy presented with coma, and a left cerebellar hemorrhage was confirmed. He underwent urgent removal of the hematoma. The removal of the cerebellar AVM was performed 10 days after the initial hemorrhage. A residual AVM was confirmed using postoperative DSA. Residual AVM was treated with SRS at 2 months postoperatively. Mild ataxia was noted in his left extremity; however, he was able to walk without assistance. He returned home.

Annual computed tomography angiography (CTA) was regularly performed. The residual AVM was confirmed using CTA 3 years 8 months after SRS (Fig. 3).

Annual CTA as surveillance imaging was scheduled. However, he did not visit our hospital in the fourth and fifth years after SRS.

CTA as surveillance imaging detected slight residual AVM regrowth 6 years 7 months after SRS. We recommended additional treatment for the residual AVM; however, the patient and his family opted for further observation.

He underwent MRI/MRA as surveillance imaging, and new aneurysm formation at the nidus was confirmed 7 years after SRS. Two days later, the patient experienced a severe headache, and rebleeding from the left cerebellum was confirmed. New aneurysm formation was not detected by DSA 1 day after rebleeding or by CTA 3 days after rebleeding (Fig. 4).

Endovascular embolization was performed 6 days after rebleeding. The main feeding arteries originated from the superior cerebellar artery. The new aneurysm formation remained unvisualized. Embolization was performed using 20% glue (n-butyl cyanoacrylate/ionized oil = 1:5) thrice via the superior cerebellar artery. The removal of AVM was performed after embolization. Intraoperatively, tight adhesions between the cerebellum and dura mater and scar tissue were confirmed that may have been related to the previous operations. The AVM was detached from the surrounding tissue and completely removed.

Despite ataxia in his left extremity, the patient was able to walk without assistance and return home again. Annual MRI/MRA surveillance imaging was scheduled, and no AVM recurrence was detected.

Discussion

Observations

We retrospectively investigated rebleeding in pediatric patients with ruptured AVMs over a long-term follow-up period. Rebleeding

FIG. 2. A: MRI T2-weighted image (T2WI) shows the hematoma cavity caused by initial bleeding in the right thalamus at 2 months after initial bleeding. B: MRI T2WI shows the hematoma cavity and residual AVM at 6 years after SRS. C: Enlarged view of the AVM. MRA shows residual AVM regrowth and new aneurysm formation (arrow) at the residual AVM in the left thalamus 21 years after SRS. D: CT shows AVM rebleeding at 8 months after new aneurysm formation. The hemorrhage spread from the left thalamus to the lateral ventricle and hematoma cavity in the right thalamus. E: Enlarged view of the AVM. CTA shows new aneurysm formation after rebleeding (arrow). F: DSA of the left vertebral artery at 6 days after rebleeding shows the new aneurysm formation associated with AVM (arrow).
was confirmed in two patients with residual AVM at 21 and 7 years after the initial rupture and treatment, respectively. In these patients, new aneurysm formation and residual AVM regrowth were confirmed before rebleeding occurred. In particular, the duration between the confirmation of new aneurysm formation and rebleeding was short (8 months and 2 days, respectively).

It is important to prevent rebleeding to preserve neurological function. A previous study reported that, in pediatric AVM, deep venous drainage and aneurysms were associated with the risk of rebleeding. Diffuse-type AVMs showed a greater likelihood of recurrence. These morphological characteristics were determined on initial angiography. Additionally, incomplete obliteration of the AVM on the last DSA was identified as a risk factor for rebleeding after the initial treatment. Therefore, complete obliteration is required to prevent rebleeding.

Notably, it is difficult to achieve complete obliteration in all patients. The immediate obliteration rate of AVMs in pediatric patients was 65%–76%. In addition, 18% of AVM cases in pediatric patients were of the diffuse type, which had a greater risk of residual lesions. Further treatments for AVM obliteration included repeat resection, repeat embolization, and combined treatment. The long-term obliteration rate was 61%–90% whereas the obliteration rate was decreased in SM grade V AVM cases. Therefore, the identification of predictors of impending rebleeding during the follow-up of the residual AVM is required to consider more appropriate types and timing of additional treatments.

AVM has traditionally been considered a congenital disease; however, it can develop after birth. A high vascular endothelial growth factor level has been implicated in AVM bleeding and rupture. Endothelial cells within the AVM are highly activated cells that overexpress proangiogenic growth factor. The dynamic characteristics of AVMs in pediatric patients have also been reported, and AVM recurrence is frequently reported in this population. Age is a major risk factor for AVM recurrence. Additionally, aneurysm development may be related to hemodynamic factors caused by the AVM.

Imaging Recommendations

The long-term imaging follow-up is recommended for AVM in pediatric patients. Aboukaïs et al. recommended that, despite complete AVM obliteration, periodic angiographic follow-up is needed. They also suggested final follow-up using three-dimensional (3D) rotational DSA at 18 years of age to detect any recurrent AVM.

In this study, rebleeding from the residual AVM occurred 20 years after the initial rupture and treatment. Therefore, if complete AVM obliteration is not achieved, long-term follow-up examinations are required, even in adulthood. New aneurysm formation and
residual AVM regrowth were detected in our patients using MRA and CTA. Therefore, we recommend annual evaluations using MRA and/or CTA. If new aneurysm formation and/or residual AVM regrowth are suspected, further investigations using DSA, including 3D rotational imaging, are recommended.

New Aneurysm Formation and Treatments

The associated aneurysm is known to be a weak point of AVM. In our cases, new aneurysm formation was detected just before rebleeding occurred. In a previous report, de novo aneurysm formation was identified soon after rebleeding from the residual AVM. However, in case 2, new aneurysm formation was not detected by DSA or CTA after rebleeding. Missing aneurysms due to thrombosis of the aneurysm after rupture have been reported, and we suspect this mechanism as the reason.

In case 2, regarding new aneurysm formation at the nidus, venous ectasia was also possible. However, it may be difficult to distinguish intranidal arterial aneurysms from intranidal venous ectasia. Venous ectasia is also a weak point of AVM. The signs of new aneurysm formation may be significant, even if it is venous ectasia, and it is important to diagnose these aneurysms before rebleeding occurs in patients with residual AVMs.

If new aneurysm formation and/or residual AVM regrowth are confirmed, further treatment is recommended. In particular, if a new aneurysm formation is detected, early aneurysm obliteration may be required. Microsurgical resection has the ability to immediately eliminate the risk of hemorrhage. A low-SM-grade AVM can be resected repeatedly as described in case 2. However, AVM resection in the deep eloquent area is risky. In case 1, the AVM was found in the bilateral thalamus. AVM resection in deep locations, including the thalamus, is associated with relatively lower obliteration rates and higher permanent neurological morbidity rates. SRS is useful in the management of these lesions, whereas repeated radiosurgery is also useful for remnant AVMs. However, the effects of SRS may not be apparent for several years after treatment. An associated aneurysm is a risk factor for rebleeding and requires urgent occlusion. The selective target embolization of aneurysms associated with AVMs could immediately lower the risk of rebleeding. However, procedural limitations and complications should be considered. The complications of embolization include ICH, ischemic stroke, and delayed postoperative AVM rupture. Despite the risk of complications, intervention is often advocated because of the significant morbidity and mortality associated with thalamic AVM rupture.

Limitations

The duration of this study was 30 years. In Japan, medical records are kept at hospitals for at least 5 years. Thus, we could not confirm all patients’ imaging data. For further studies, the use of the electronic medical record system will help to keep the data on record longer than paper-based medical records. In addition, we also evaluated only a small number of patients. To investigate the detailed process of new aneurysm formation and residual AVM regrowth to rebleeding, we will continue our investigation using an electronic medical record system with a larger number of patients. We plan to investigate the detailed angioarchitecture of the AVM using 3D rotational DSA images.

Lessons

Complete obliteration of ruptured AVM is the ideal treatment strategy. However, if it is difficult to achieve, residual AVM rebleeding can occur >20 years after initial rupture and treatment. Aneurysm formation and residual AVM regrowth were detected prior to rebleeding in the two cases described here. Therefore, new aneurysm formation and residual AVM regrowth may be important predictors of rebleeding that require additional treatment.

Acknowledgments

We are grateful to Kyoko Ninomiya and Takaharu Ushijima for their assistance with this study.

References

1. Beslow LA, Licht DJ, Smith SE, et al. Predictors of outcome in childhood intracerebral hemorrhage: a prospective consecutive cohort study. Stroke. 2010;41(2):313–318.
2. Meyer-Heim AD, Boltshauser E. Spontaneous intracranial hemorrhage in children: etiology, presentation and outcome. Brain Dev. 2003;25(6):416–421.
3. Blauwblomme T, Bourgeois M, Meyer P, et al. Long-term outcome of 106 consecutive pediatric ruptured brain arteriovenous malformations after combined treatment. Stroke. 2014;45(6):1664–1671.
4. van Beijnum J, van der Worp HB, Buis DR, et al. Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. JAMA. 2011;306(18):2011–2019.
5. Klimo P Jr, Rao G, Brockmeyer D. Pediatric arteriovenous malformations: a 15-year experience with an emphasis on residual and recurrent lesions. Childs Nerv Syst. 2007;23(1):31–37.
6. Aboukaïs R, Vinchon M, Quiedet M, Bourgeois P, Leclerc X, Lejeune JP. Reappearance of arteriovenous malformations after complete resection of ruptured arteriovenous malformations: true recurrence or false-negative early postoperative imaging result? J Neurosurg. 2017;126(4):1088–1093.

7. Morgan MK, Patel NJ, Simons M, Ritson EA, Heller GZ. Influence of the combination of patient age and deep venous drainage on brain arteriovenous malformation recurrence after surgery. J Neurosurg. 2012;117(5):934–941.

8. Bristol RE, Albuquerque FC, Spetzler RF, Rekate HL, McDougall CG, Zabramski JM. Surgical management of arteriovenous malformations in children. J Neurosurg. 2006;105(2 suppl):88–93.

9. Florian IA, Beni L, Moisoiu V, et al. ‘De novo’ brain AVMs-hypotheses for development and a systematic review of reported cases. Medicina (Kaunas). 2021;57(3):201.

10. Cheng P, Ma L, Shaligram S, et al. Effect of elevation of vascular endothelial growth factor level on exacerbation of hemorrhage in mouse brain arteriovenous malformation. J Neurosurg. 2019;132(5):1566–1573.

11. Jabbour MN, Elder JB, Samueleson CG, et al. Aberrant angiogenic characteristics of human brain arteriovenous malformation endothelial cells. Neurosurgery. 2009;64(1):139–148.

12. Rammos SK, Gardenghi B, Bortolotti C, Cloft HJ, Lanzino G. Aneurysms associated with brain arteriovenous malformations. AJNR Am J Neuroradiol. 2016;37(11):1966–1971.

13. Krings T, Hans FJ, Gelbprasert S, Terbrugge K. Partial “targeted” embolisation of brain arteriovenous malformations. Eur Radiol. 2010;20(11):2723–2731.

14. Signorelli F, Gory B, Pelissou-Guyotat I, et al. Ruptured brain arteriovenous malformations associated with aneurysms: safety and efficacy of selective embolization in the acute phase of hemorrhage. Neuroradiology. 2014;56(9):763–769.

15. Howard BM, Hu R, Barrow JW, Barrow DL. Comprehensive review of imaging of intracranial aneurysms and angiographically negative subarachnoid hemorrhage. Neurosurg Focus. 2019;47(6):E20.

16. Derdeyn CP, Zipfel GJ, Albuquerque FC, et al. Management of brain arteriovenous malformations: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2017;48(8):e200–e224.

17. Chen CJ, Kearns KN, Ding D, et al. Stereotactic radiosurgery for arteriovenous malformations of the basal ganglia and thalamus: an international multicenter study. J Neurosurg. 2019;132(1):122–131.

18. Buis DR, Meijer OW, van den Berg R, et al. Clinical outcome after repeated radiosurgery for brain arteriovenous malformations. Radiother Oncol. 2010;95(2):250–256.

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Matsumoto, Nagata, Hashikawa, Sakai, S Takahashi, Sugita. Acquisition of data: Matsumoto, Sakai, Hashimoto, Sugita. Analysis and interpretation of data: Matsumoto, Sakai, Hashikawa, Sugita. Drafting the article: Matsumoto, Sugita. Critically revising the article: Matsumoto. Reviewed submitted version of manuscript: Matsumoto, Nakagawa. Approved the final version of the manuscript on behalf of all authors: Matsumoto. Statistical analysis: Matsumoto. Administrative/technical/material support: Matsumoto, Hashikawa, Sakai, Goto. Study supervision: Matsumoto, Hashikawa, Sakai, K Takahashi.

Correspondence
Yoshihisa Matsumoto: St. Mary’s Hospital, Fukuoka, Japan. fwip4873@nifty.com.