Natural History of De Novo Aneurysm Formation in Patients with Treated Aneurysmatic Subarachnoid Hemorrhage: A Ten-Year Follow-Up

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■ BACKGROUND: **De novo aneurysm formation after completely occluded aneurysms via clipping or coiling has not been well studied. Although known to occur several years after initial aneurysm management, the natural history of de novo aneurysms is obscure. We investigated the formation of new aneurysms in patients who had previously undergone treatment of intracranial aneurysms.**

■ METHODS: **In a retrospective, single-institutional series, eligible patients who had undergone treatment of ruptured cerebral aneurysms from 2000 to 2011 were included. The primary outcome measure was the development of de novo aneurysms during long-term follow-up.**

■ RESULTS: **Overall, 130 patients (63% women) who had undergone microsurgical clipping (n = 63; 48.5%) or endovascular coiling (n = 67%; 51.5%) for ruptured aneurysms were included. The average follow-up time for our cohort was 10 ± 2.7 years. De novo aneurysms occurred in 10 of 130 patients (7.7%), with a mean time of 7.9 years for aneurysm detection. No association between the formation of de novo aneurysms and the location of the treated aneurysms, smoking status, hypertension, age, or gender was found. Follow-up imaging studies were performed every 2 years. De novo aneurysms had formed in 2 patients within 2–5 years, 7 patients after 5–10 years, and 1 patient after 10 years of follow-up. In 2 of 10 patients, the de novo aneurysm had ruptured and led to subarachnoid haemorrhage.**

■ CONCLUSION: **The rate of de novo aneurysm occurrence was 7.6%, with a mean time to development of 7.9 years. This underscores the significance of long-term monitoring of patients with intracranial aneurysms. In our series, most new aneurysms had occurred after 5 years of follow-up.**

INTRODUCTION

Subarachnoid hemorrhage (SAH) affects ~1 of 10,000 people annually and has been associated with a high mortality rate of up to 50% within 1 month after occurrence. The potential source of bleeding is almost always linked to an aneurysmal rupture from an underlying cerebral artery. Microsurgical clipping and coiling with the evolution of endovascular techniques have formed the mainstay treatment for these patients.[1] Despite the high success rate in achieving aneurysm occlusion at the concerned location, neither of these treatment modalities preclude new or "de novo" aneurysm formation at a distinct location from the initial pathologic occurrence.

De novo aneurysm formation after completely occluded aneurysms via clipping or coiling has not been well studied but is known to occur after several years, independently of the initial aneurysm development.[2,3] With limited longitudinal studies on the topic documenting long-term follow-up data, we report our findings from a long-term follow-up investigation of patients who had undergone treatment of aneurysmal SAH and experienced de novo aneurysm formation. With a mean follow-up period of >10

Key words
- Cerebral aneurysm
- Cerebrovascular
- De novo aneurysm
- Endovascular coiling
- Microsurgical clipping
- Subarachnoid haemorrhage

Abbreviations and Acronyms
SAH: subarachnoid haemorrhage

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Citation: World Neurosurg. (2019) 122:e291-e295. https://doi.org/10.1016/j.wneu.2018.10.022

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

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

1878-8750/$ - see front matter

years, we aimed to provide insights on the natural history of de novo aneurysm formation and the stability of previously treated aneurysms.

METHODS

In a retrospective, single-institutional series, we included eligible patients who had undergone treatment of ruptured cerebral aneurysms from 2000 to 2011. Follow-up examinations continued until November 2017. The examinations included digital subtraction angiography 6 months after the initial treatment, followed by magnetic resonance angiography for coiled aneurysms, and computed tomography angiography for aneurysms that had been treated by clipping every 2 years. In our study, we focused on patients who had undergone regular follow-up examinations and whose ruptured aneurysm had been completely occluded. Patients who had died within the first year after SAH ($n = 480$), those who had undergone repeat treatment ($n = 266$ for revision coiling), those with inadequate imaging requirements ($n = 250$), and those who had been lost to follow-up ($n = 74$) were excluded from analysis. The algorithm for cohort selection is depicted in Figure 1.

Data on patient demographics and imaging parameters were extracted from the patients' medical records. During the follow-up period, the formation of de novo aneurysms was the primary outcome measure. A subgroup analysis of those who had undergone microsurgery versus those who had undergone endovascular aneurysm management was performed. Adult patients (aged >18 years) with routine neuroimaging were included. The potential risk factors for de novo aneurysms, such as age, gender, nicotine abuse (smoking), hypertension, multiple aneurysms, and family history, were evaluated. Categorical variables across the 2 intervention groups (microsurgical clipping vs. endovascular coiling) were compared using Pearson's χ^2 test, and differences in metric values were assessed using the independent samples t test. All statistical tests were 2-tailed, and the significance level was set at a type I error corresponding to 5%. The local ethics committee study approved the present study (approval number, 5919R). All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

RESULTS

Study Cohort

Overall, 1200 patients with an aneurysmatic SAH were treated in our center from 2000 to 2011. Using our inclusion criteria, 130 patients were deemed eligible and were included for analysis. Of the 130 patients, 63 (48.5%) were treated by microsurgical clipping for 73 aneurysms and 67 (51.5%) by endovascular coiling (77 aneurysms). The mean follow-up period for the 130 patients in our cohort was 10 ± 2.7 years (range, 6–17).

Patient Characteristics

The mean patient age in the microsurgical group was 48.9 ± 10.6 years (range, 15–64) and 50.1 ± 12.6 years (range, 12–71) in the endovascular group. Overall, the cohort included 82 women (63.1%) and 48 men (36.9%). Of the 130 patients, 55 (42.3%) had hypertension and 18 (13.8%) were smokers. No differences were noted between the patients in the microsurgical clipping versus

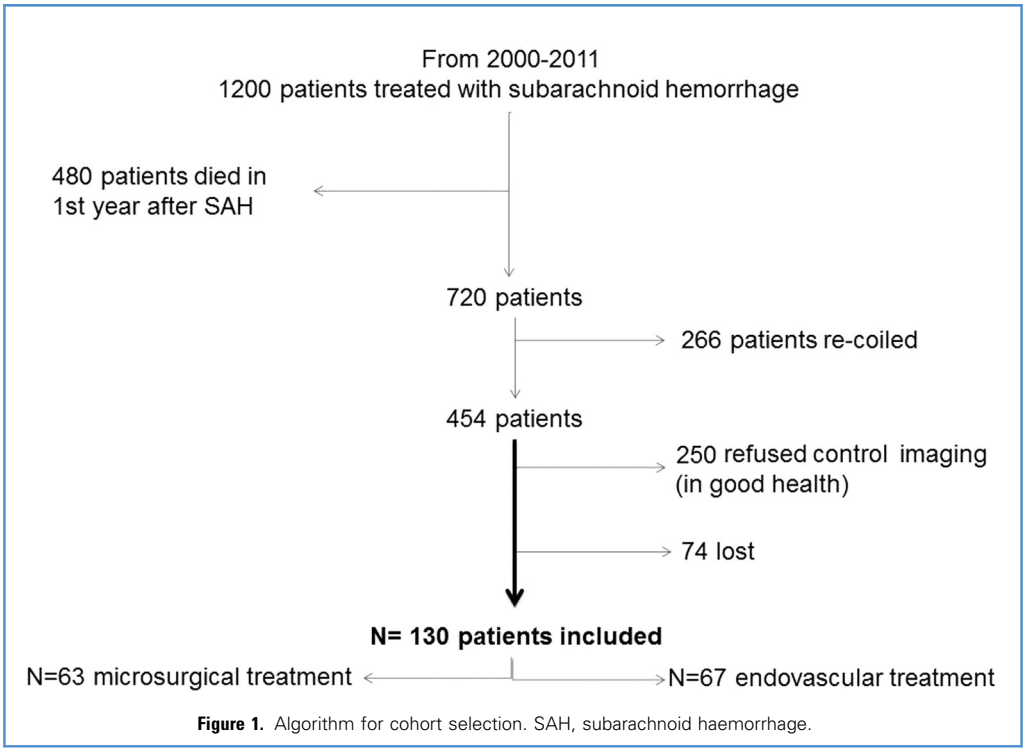

Figure 1. Algorithm for cohort selection. SAH, subarachnoid haemorrhage.

endovascular coiling group in terms of age (P = 0.559), gender (P = 0.924), hypertension (P = 0.348), and smoking status (P = 0.713). The mean follow-up period was 10.1 ± 2.78 years (median, 10; range, 6–17) for the microsurgical group and 10.4 ± 2.6 years (median, 11; range, 6–15) for the endovascular group. The procedural complication rate in the microsurgical group was 11.1% (n = 7) and included repeat bleeding in 1 patient (1.6%) and infarction in 6 patients (9.5%). In the endovascular group, the procedural complication rate was 6.0% (n = 4). All 4 patients had experienced infarctions, not related to vasospasms. No statistical significance was noted in terms of the complication rates between the microsurgical and endovascular groups. An overview of patient characteristics is presented in Table 1.

The overall distribution of aneurysms in our series is depicted in Figure 2. The breakdown of the anatomical location of these aneurysms treated via microsurgical clipping or endovascular coiling is presented in Figure 3. Most aneurysms were in the anterior communicating and middle cerebral artery (Figure 2). Almost two thirds of the anterior communicating artery aneurysms were treated endovascularly, all middle cerebral aneurysms were treated by microsurgical clipping, and all basilar artery aneurysms using endovascular coiling (Figure 3).

De Novo Aneurysm Formation (Primary Outcome)

Overall, 10 patients (7.7%) developed new aneurysms (de novo) at locations that differed from those of the treated ruptured aneurysms. The mean interval to de novo aneurysm formation after the treated aneurysmatic subarachnoid hemorrhage was 7.9 ± 2.9 years (range, 4–14). Two patients presented with de novo aneurysms within the first 5 years after the initial bleeding episode. Seven patients developed new aneurysms after 5 years, and only 1 patient presented with a new aneurysm after 10 years from the initial subarachnoid bleeding episode. Of the 10 patients with de novo aneurysm formation, 2 experienced a rupture of the de novo aneurysm that led to SAH. Of the 10 patients with de novo aneurysms, 6 (60%) had hypertension compared with 45 of 120 patients (37.5%) without new aneurysm formation. Nicotine abuse was reported in 3 of the 10 patients with new aneurysms (30%) and in 14 of the 120 patients without de novo aneurysms (11.6%). No statistically significant correlation was found for hypertension or nicotine abuse and new aneurysm formation. Also, no correlation was found for gender, age, location of the treated aneurysms, and presence of multiple aneurysms at the beginning of the follow-up period.

Table 1. Patient Characteristics (n = 130)

Characteristic	Microsurgical Clipping (n = 63)	Endovascular Coiling (n = 67)	P Value
Age (years)	48.9 ± 10.6	50.1 ± 12.6	0.559
Gender			
Female	40 (63.5)	42 (62.7)	0.924
Male	23 (36.5)	25 (37.3)	
Hypertension	24 (38.1)	31 (46.3)	0.348
Smoking	8 (12.7)	10 (14.9)	0.713
Complications	7 (11.1)	4 (6.0)	0.355*
Repeat bleeding	1 (1.6)	0 (0.0)	0.485*
Infarction	6 (9.5)	4 (6.0)	0.522*
Follow-up (years)	10.1 ± 2.78	10.4 ± 2.6	0.526

Data presented as mean ± standard deviation or n (%).
*P values derived from Fisher's exact test.

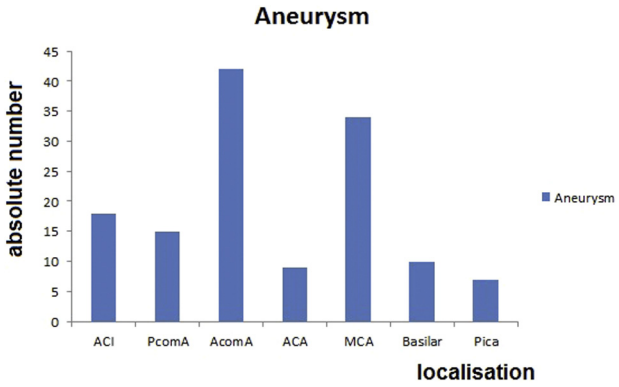

Figure 2. Absolute number of locations of the studied aneurysms. ACA, anterior cerebral artery; ACI, internal carotid artery; AcomA, anterior communicating artery; MCA, middle cerebral artery; PcomA, posterior communicating artery.

DISCUSSION

Aneurysm formation is an ongoing process influenced by genetic predisposition and several potential risk factors. With advancements in neuroimaging techniques and the advent of endovascular coiling, most cerebral aneurysms can be managed with optimal clinical outcomes using either microsurgical clipping or endovascular coiling. Several studies have evaluated long-term outcomes in the management of cerebral aneurysms and contrasted

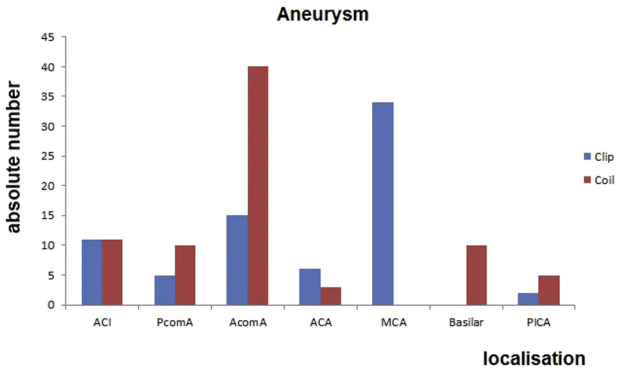

Figure 3. Number of aneurysms treated by clipping or coiling in the present study.

efficacy of dual modalities (clipping vs. coiling), albeit with variable outcomes. Although these studies have contributed to the understanding of the natural history of cerebral aneurysms, limited data are available on the natural history of de novo aneurysms formation and complications after treatment of initial aneurysms. In the present study, we investigated the formation of de novo aneurysms in a large cohort of patients who had undergone treatment for their initial ruptured aneurysms and reported the findings from long-term follow-up examinations.

Based on our series, the rate of de novo formation at an average follow-up period of >10 years (range, 6–17) was 7.7% and, to the best of our knowledge, is 1 of the longest follow-up periods in the reported data. In a study of 616 patients with 926 aneurysms (n = 758 clipped [81.9%]), Brown et al.[4] reported de novo aneurysm formation in 0.97% of their patients at a follow-up period of 1–23 years. In contrast, Zali et al.[5] and Burkhardt et al.[3] reported a 4.5% and 3.3% rate of de novo aneurysm formation in patients undergoing microsurgical clipping, respectively. In a long-term follow-up period of >10 years, similar to the longitudinal monitoring time in our study, Bruneau et al.[6] reported a de novo aneurysm formation rate as great as 30% in their series of 20 patients.

Rahmah et al.[7] reported that female gender and hypertension contribute to de novo aneurysm formation, with a mean time of occurrence of 10.6 years. In our series, hypertension and nicotine abuse was greater; however, the difference was not statistically significant between the patients with de novo aneurysms and those without de novo aneurysms. Juvela et al.[8] found female gender and cigarette smoking to be potential risk factors for de novo aneurysm formation. Sakaki et al.[9] reported 9 de novo cases in a series of almost 1000 patients who had been treated for aneurysms. All 9 patients had hypertension; however, the number was too small to draw valid associations.[9] A family history of subarachnoid bleeding should not be disregarded in the case of de novo aneurysm.[10] In a meta-analysis performed from pooling nearly 15,000 aneurysms from 35 clinical studies, Giordan et al.[11] noted smoking, the presence of multiple aneurysms, positive family history, and female gender as potential risk factors for de novo aneurysm formation.[11] However, the statistical significance noted for ≥1 of the risk factors was reported in only a few studies, with others reported no such significance. In our study, we did not find any potential risk factors for de novo aneurysm formation. One plausible, but possibly not the single, explanation could be that we had excluded many patients from the analysis by our stringent inclusion criteria. However, our findings regarding the mean interval to the discovery of de no aneurysms are in alignment with the meta-analysis reported by Giordan et al.,[11] which noted an average time of 10 years for patients with a previous rupture. In another relevant meta-analysis of nearly 6400 patients, Hu et al.[12] noted female gender, age <40 years, smoking, positive family history, multiple aneurysms, and internal carotid artery location as risk factors warranting vigilance for de novo aneurysms.

Despite the obvious merit of our study, including the long-term follow-up duration, potential limitations were present that warrant elaboration. Also, our study does not reflect differences in recurrence or de novo formation rates between partially versus completely coiled aneurysms, as reported in previous studies.[13] This was primarily because partially occluded aneurysms were excluded by our inclusion criteria. The incidence rate of de novo aneurysm formation in patients with a history of ruptured aneurysms according to Giordan et al.[11] is not significantly different from that for those with no previous bleeding. Thus, the fact that we excluded the partially occluded aneurysms should not pose a limitation. The coiled aneurysms included in our study were all without a stent. The rate of de novo aneurysm formation could be affected by the contemporary practice of using stent-assisted coiling or flow diverters. However, limited data are available demonstrating the benefits of stent-assisted treatment compared with microsurgical clipping in long-term follow-up. In addition to the inherent selection bias considering the retrospective, single-institutional design, the lack of potential comorbidities could have potentially affected the risk factor assessment for de novo aneurysms. In the absence of time-series analysis, the possibility of changes in the risk factors over time (e.g., patients quitting smoking during the follow-up time), the possibility of these factors on the aneurysm formation estimates could not be ruled out. Owing to our decision to focus on patients with regular follow-up data whose initially ruptured aneurysm had been completely occluded, our numbers were smaller than those in some other studies. The relatively small amount of cases could have been why no statistically significant risk factor could be identified.

CONCLUSION

In on our series, we noted de novo aneurysms in 7.7% of patients who had been previously treated using microsurgical clipping or endovascular coiling for aneurysmal SAH in a follow-up period averaging >10 years. Most of these de novo aneurysms occurred 5–10 years after the initial bleeding episode. In our series, we could not find any statistically significant risk factors for the formation of de novo aneurysms. Combining our experience with the knowledge from recent meta-analyses, we recommend follow-up imaging studies every 2 years at least for 10 years after the SAH.

REFERENCES

1. Long B, Koyfman A, Runyon MS. Subarachnoid hemorrhage: updates in diagnosis and management. *Emerg Med Clin North Am*. 2017;35:803-824.

2. Briganti F, Cirillo S, Caranci F, Esposito F, Maiuri F. Development of "de novo" aneurysms following endovascular procedures. *Neuroradiology*. 2002;44:604-609.

3. Burkhardt JK, Chua MHJ, Weiss M, Do ASS, Winkler EA, Lawton MT. Risk of aneurysm residual regrowth, recurrence, and de novo aneurysm formation after microsurgical clip occlusion based on follow-up with catheter angiography. *World Neurosurg*. 2017;106:74-84.

4. Brown MA, Parish J, Guandique CF, Payner TD, Horner T, Leipzig T, et al. A long-term study of durability and risk factors for aneurysm recurrence after microsurgical clip ligation. *J Neurosurg*. 2017;126:819-824.

5. Zali A, Khoshnood RJ, Zarghi A. De novo aneurysms in long-term follow-up computed tomographic angiography of patients with clipped intracranial aneurysms. *World Neurosurg*. 2014;82:722-725.

6. Bruneau M, Rynkowski M, Smida-Rynkowska K, Brotchi J, De Witte O, Lubicz B. Long-term

follow-up survey reveals a high yield, up to 30% of patients presenting newly detected aneurysms more than 10 years after ruptured intracranial aneurysms clipping. *Neurosurg Rev*. 2011;34:485-496.

7. Rahmah NN, Horiuchi T, Kusano Y, Sasaki T, Hongo K. De novo aneurysm: case reports and literature review. *Neurosurgery*. 2011;69:E761-E766 [discussion: E766-E767].

8. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. *Stroke*. 2001;32:485-491.

9. Sakaki T, Tominaga M, Miyamoto K, Tsunoda S, Hiasa Y. Clinical studies of de novo aneurysms. *Neurosurgery*. 1993;32:512-516 [discussion: 516-517].

10. Lebland R. De novo formation of familial cerebral aneurysms: case report. *Neurosurgery*. 1999;44:871-876 [discussion: 876-877].

11. Giordan E, Lanzino G, Rangel-Castilla L, Murad MH, Brinjikji W. Risk of de novo aneurysm formation in patients with a prior diagnosis of ruptured or unruptured aneurysm: systematic review and meta-analysis. *J Neurosurg*. 2018:1-11.

12. Hu S, Yu N, Li Y, Hao Z, Liu Z, Li MH. A meta-analysis of risk factors for the formation of de novo intracranial aneurysms [e-pub ahead of print]. *Neurosurgery*. https://doi.org/10.1093/neuros/nyy332, accessed July 30, 2018.

13. Consoli A, Renieri L, Mura R, Nappini S, Ricciardi F, Pecchioli G, et al. Five to ten years follow-up after coiling of 241 patients with acutely ruptured aneurysms: a single centre experience. *Interv Neuroradiol*. 2012;18:5-13.

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Received 8 May 2018; accepted 3 October 2018

Citation: World Neurosurg. (2019) 122:e291-e295. https://doi.org/10.1016/j.wneu.2018.10.022

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