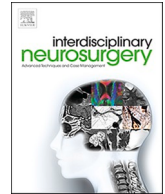




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Research Article

Risk factors for recurrence after coil embolization for internal carotid artery-posterior communicating artery aneurysms

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ABSTRACT

Background: Use of coil embolization for internal carotid artery-posterior communicating artery aneurysms (IC-PC ANs) has been increasing. However, the recurrence rate after embolization is rather high compared to that after surgery. The aim of this study was to evaluate the factors related to recurrence after coil embolization for IC-PC ANs.

Methods: A total of 69 patients with IC-PC ANs treated with coil embolization between 2013 and 2019 were retrospectively enrolled, and we evaluated whether the aneurysms recurred after embolization. The patients were divided into two groups (no-recurrence group and recurrence group), and the relationships of several patient or aneurysm characteristics and treatment-related information with aneurysm recurrence were examined.

Results: Twenty patients (29%) developed aneurysm recurrence. There were significant differences in dome size (5.19 mm/6.48 mm, $p = 0.01$), neck width (3.25 mm/4.23 mm $p = 0.009$), aneurysm volume (47.5 mm³/120 mm³, $p = 0.003$), and Pcom diameter (1.11 mm/1.96 mm $p = 0.005$) between the two groups. Pcom diameter was the independent risk factor for recurrence (odds ratio: 3.52, 95%CI 1.43–8.69, $p = 0.006$). The cutoff for Pcom diameter as the factor related to recurrence was 1.79 mm, with sensitivity of 60% and specificity of 83.7%.

Conclusion: In this study, dome size, neck width, aneurysm volume, and Pcom diameter were associated with recurrence after coil embolization for IC-PC ANs. In particular, Pcom diameter could be an independent risk factor for recurrence.

1. Introduction

Internal carotid artery-posterior communicating artery aneurysms (IC-PC ANs) are the second most common of all intracranial aneurysms, accounting for about 25% of all cases [1]. The International Study of Unruptured Intracranial Aneurysms (ISUIA) reported that the rupture rate of posterior circulation aneurysms including IC-PC ANs was higher than that of anterior circulation aneurysms [2], and the natural course of Unruptured Cerebral Aneurysms in a Japanese cohort (UCAS Japan)

study showed that an IC-PC AN is a risk factor for rupture [3]. Thus, regarding IC-PC ANs, not only ruptured cases, but also unruptured cases may be considered for treatment if there are risk factors for rupture. The effectiveness and safety of coil embolization for intracranial aneurysms are proven, and cases of coil embolization have been increasing [4]. On the other hand, one of the disadvantages of coil embolization is the higher recurrence rate compared to surgical clipping [4–6]. The International Subarachnoid Aneurysm Trial (ISAT) found that coil embolization has a 6.9 times retreatment risk compared with surgical clipping

Abbreviations: IC-PC, internal carotid artery-posterior communicating artery; AN, aneurysm; Pcom, posterior communicating artery; ISUIA, The International Study of Unruptured Intracranial Aneurysms; UCAS Japan, Unruptured Cerebral Aneurysms in a Japanese cohort; ISAT, The International Subarachnoid Aneurysm Trial; DSA, Digital subtraction angiography; CO, complete occlusion; NR, neck remnant; DF, dome filling; ROC, curve, receiver operating characteristic curve; AUC, area under the curve.

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[7]. If the risk factors for recurrence after coil embolization for IC-PC ANs could be clarified, they might become useful predictors for not only follow-up after treatment, but also for selecting the treatment modality. In the present study, the patients who had undergone coil embolization for IC-PC ANs in our facility were retrospectively analyzed, and the risk factors for recurrence were assessed.

2. Methods

This was a case-control study in a single center. Patients with IC-PC ANs treated with coil embolization in our facility between April 2013 and August 2019 were retrospectively analyzed, and postoperative recurrence was evaluated. The patients who had previously undergone coil embolization or clipping for the target aneurysms or had not undergone follow-up angiography were excluded. Digital subtraction angiography (DSA) was performed using a SIEMENS Artis zee biplane (SIEMENS Healthcare, Forchheim, Germany), and SIEMENS syngo X-Workplace VB21, which was attached to the instrument, was used for measurement of the examination items. The patients were divided into two groups based on the findings of follow-up angiography about 6 months after embolization, the no-recurrence group and the recurrence group. The patients' medical records and imaging data were reviewed and collected.

This was an observational study that retrospectively analyzed anonymized patient information; thus, written, informed consent was not required from the patients. Institutional ethics committee approval was granted, and all procedures complied with current ethical guidelines. Opt-out materials were posted on-line, and patients who refused study participation were excluded, and their information was discarded.

2.1. Treatment procedures and follow-up

The patients were started on dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg per day, 14 days before coil embolization. All operative procedures were performed with the patients under general anesthesia. Patients received systematic heparinization, and the activated clotting time was prolonged to between 200 and 300 s. In general, simple technique was used, but, if needed, balloon remodeling or stent-assisted technique was added. When stent-assisted technique was performed, dual antiplatelet therapy was continued for at least 6 months after embolization, and it was then reduced to single antiplatelet therapy; antiplatelet therapy was finally stopped at an appropriate time depending on the patient. All patients underwent follow-up angiography 6 months after embolization, and in cases of suspected recurrence on MRI/A after that time, angiography was performed each time.

2.2. Examination items

As potential risk factors for recurrence, age, sex, clinical presentation (ruptured or non-ruptured), dome size, neck width, dome-to-neck ratio, aneurysm volume, Pcom variation (fetal type, adult type, and hypoplastic type), Pcom diameter, and whether the Pcom branched from the aneurysm were analyzed. The factors related to the operation itself were the degree of embolization just after the procedure, with or without stent assistance, and whether the Pcom was sacrificed. Regarding Pcom variations, fetal type is an artery mainly feeding the posterior cerebral artery and larger than P1; the hypoplastic type is not apparent on angiography; and other than those is the adult type. The degree of embolization was classified into three categories according to the Raymond-Roy classification [8]: complete occlusion (CO) is no filling of the aneurysm; neck remnant (NR) is partial filling of just the neck, but not the dome; and dome filling (DF) is partial filling of the dome. Recurrence was defined as increased flow of contrast agent into the aneurysm compared with just after embolization, and the angiographic findings were independently evaluated by both the examining neuro-interventionalist and the first author.

2.3. Statistical analysis

Continuous variables are expressed as medians (IQR, interquartile ranges), and categorical variables are presented as numbers and percentages. All statistical analyses were performed using EZR on R commander Version 1.40, which is a modified version of R commander designed to add statistical functions frequently used in biostatistics [9]. Comparisons between groups were performed using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. A *p* value <0.05 was considered significant. Three of the variables, which had *p* values <0.20 on univariate analysis, were entered into the multivariate logistic regression analysis. Odds ratios and 95% CIs were calculated for each of the potential risk factors for recurrence with a significant difference. To determine the cutoff value for recurrence, a receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was measured. The cutoff value was set as the point with the maximum sum of sensitivity and specificity.

3. Results

A total of 82 patients with IC-PC ANs that had been treated with coil embolization in our facility between April 2013 and August 2019 were enrolled in this study. Four patients who had previously undergone surgery of the target aneurysms, and 9 patients who did not undergo follow-up angiography were excluded, and 69 patients were finally evaluated. The baseline characteristics of the patients and the aneurysms are shown in Table 1. The median observation period was 369 days (average 605.1 days, maximum 1667 days, minimum 151 days). The patients were divided into two groups: the no-recurrence group (*n* = 49; 71%) and the recurrence group (*n* = 20; 29%). There were no

Table 1

Patient characteristics and aneurysm variables in the no-recurrence and recurrence groups.

Characteristic/ Variable	Total (<i>n</i> = 69)	No-recurrence (<i>n</i> = 49)	Recurrence (<i>n</i> = 20)	P value
	<i>n</i> or median (IQR)	<i>n</i> or median (IQR)	<i>n</i> or median (IQR)	
Age (y)	66 (52–75)	66 (48–75)	67 (60–73)	0.66
Sex, male	15 (22)	10 (20)	5 (25)	0.75
Clinical presentation				0.43
Ruptured	26 (38)	17 (35)	9 (45)	
Non-ruptured	43 (62)	32 (65)	11 (55)	
Aneurysm				
Dome size (mm)	5.3 (4.0–6.4)	5.2 (3.7–6.0)	6.5 (4.7–8.3)	0.006
Neck width (mm)	3.4 (2.7–4.3)	3.3 (2.6–4.2)	4.2 (3.0–4.8)	0.009
Dome-to-neck ratio	1.5 (1.2–1.8)	1.45 (1.2–1.7)	1.6 (1.1–1.8)	0.70
Aneurysm volume (mm ³)	55 (34–120)	48 (32–86)	120 (47–259)	0.003
Pcom variation				
Fetal type	27 (39)	16 (33)	11 (55)	0.11
Adult type	35 (51)	29 (59)	7 (35)	0.11
Hypoplastic type	6 (8.7)	4 (8.2)	2 (10)	1.0
Pcom diameter (mm)	1.3 (0.8–1.8)	1.1 (0.6–1.7)	2.0 (1.2–2.3)	0.005
Pcom branched from dome	14 (20)	7 (14)	7 (35)	0.095
Initial result				0.82
CO	39 (57)	28 (57)	11 (55)	
NR	16 (23)	12 (24)	4 (20)	
DF	14 (20)	9 (18)	5 (25)	
Stent-assisted technique	12 (17)	11 (22)	1 (5.0)	0.16
Sacrificed Pcom	5 (7.2)	3 (6.1)	2 (10)	0.62

CO, complete occlusion, NR: neck remnant, DF: dome filling.

patients with symptomatic complications of embolization and rupture of the target aneurysm during follow-up. Additional treatments were performed in 11 of 20 patients with recurrence. Two patients underwent surgical clipping, and 9 patients underwent coil embolization as additional treatment. One patient who underwent additional coil embolization for recurrence developed repeated recurrences, and neck clipping was finally performed, after which no recurrence occurred (illustrative case).

As factors related to aneurysms, dome size, neck width, and aneurysm volume all showed significant differences between the no-recurrence group and the recurrence group. On the other hand, there was no significant difference in the dome-neck-ratio between the two groups. No significant difference was noted in Pcom variations, but Pcom diameter was significantly greater in the recurrence group than in the no-recurrence group.

On multivariate analysis of the three variables with p values <0.20 (dome size, neck width, and Pcom diameter), Pcom diameter was the factor significantly related to recurrence (Table 2). The ROC curve for Pcom diameter is shown in Fig. 1. The cutoff Pcom diameter for recurrence was 1.79 mm, with sensitivity of 60%, specificity of 83.7%, and AUC of 0.719 (95%CI 0.57–0.87).

3.1. Illustrative case

A case of non-ruptured IC-PC AN is described (Fig. 2A, B). The Pcom was fetal type, and dome size, neck width, aneurysm volume, and Pcom diameter were 8.26 mm, 5.13 mm, 318.8 mm³, and 2.19 mm, respectively. Coil embolization with balloon remodeling technique was performed, with complete occlusion immediately after embolization (Fig. 2C). However, dome filling was observed on angiography 4 months after the first procedure (Fig. 2D). The second procedure with simple technique was performed and ended with complete occlusion (Fig. 2E). Eleven months after the first procedure, coil compaction was observed (Fig. 2F). Thus, additional coil embolization was performed with stent-assisted technique, in which a Neuroform Atlas 4.5 × 30 mm² (Stryker Neurovascular, CA, USA) was placed in the internal carotid artery to Pcom (Fig. 2G). Nevertheless, 4 months after the last embolization, follow-up angiography showed recurrence (Fig. 2H). Finally, surgical clipping was performed 23 months after initial embolization, and there has been no recurrence since then (Fig. 2I, J).

4. Discussion

In this study, various factors related to recurrence of coil embolization for IC-PC ANs were analyzed. There were significant differences in dome size, neck width, aneurysm volume, and Pcom diameter between the recurrence and no-recurrence groups. In particular, Pcom diameter was the risk factor significantly related to recurrence after coil embolization on multivariate analysis. Previous studies have shown that characteristics such as a large dome or wide neck were the risk factors for recurrence after coil embolization [7,10–16], and they concluded that the reason why aneurysms with these characteristics frequently recurred was that it was difficult to achieve complete occlusion [13]. In contrast, the present result did not show a significant difference in the rate of complete occlusion between the two groups. This suggests that there might be no reasons for recurrence other than incomplete occlusion. The risk factors for recurrence identified in the present study

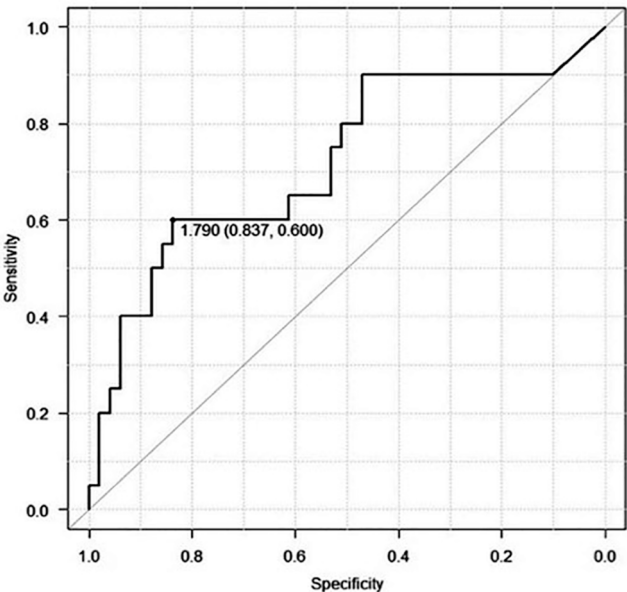


Fig. 1. Receiver operating characteristic (ROC) curve of Pcom diameter as a factor related to recurrence. AUC = 0.719 (95%CI 0.57–0.87), Sensitivity 60% and Specificity 83.7%

(dome size, neck width, and aneurysm volume) are aneurysm-specific characteristics, and these characteristics could be related to blood flow into aneurysms. Luo et al. examined the risk factors for recurrence after coil embolization using computational fluid dynamics analysis, which showed that the pressure caused by high-speed blood flow may lead to coil compaction in an aneurysm, especially one with a wide neck [17], and it is thought to be a factor related to recanalization. This is consistent with the present analysis. Thus, aneurysms with a large dome or a wide neck might have a risk of recurrence even if they showed complete occlusion after the procedure.

Pcom diameter was found to be a risk factor for recurrence after coil embolization, and this suggests that Pcom development could affect the blood flow dynamics in aneurysms. The hemodynamics of IC-PC ANs with a large Pcom are expected to be similar to those of the bifurcation-type aneurysm from the viewpoint of blood distribution into the internal carotid artery and a large Pcom, whereas the hemodynamics of IC-PC ANs with a small Pcom are similar to those of a sidewall-type aneurysm. A previous study found that progressive thrombosis in aneurysms after coil embolization was frequently observed in sidewall-type aneurysms [18]. Songsaeng et al. [19] reported that the hemodynamic impact on the aneurysm with coil embolization determines long-term stability, and that sidewall-type aneurysms may experience less hemodynamic stress than terminal-type aneurysms. Additionally, with respect to anatomical variation, a small Pcom may lead to less turbulence due to flow diversion, and less recanalization occurred. Felicitas et al. reported that bifurcation-type aneurysms had concentrated and complex flow and higher rupture rates than sidewall-type aneurysms, as for IC-PC ANs [20]. For these reasons, IC-PC ANs with a large Pcom have hemodynamic stress due to the turbulence in the aneurysms themselves, which might lead to recurrence after embolization.

The present study showed that Pcom diameter is one of the risk factors related to recurrence after coil embolization for IC-PC ANs. Though the cutoff of Pcom diameter for recurrence was determined, this result might not be highly reliable because of the small AUC. Although this might not be a stable predictor because of the retrospective nature of the study, it is useful to consider Pcom diameter in combination with the other factors, such as dome neck, neck width, ruptured status, and fetal type. These risk factors are likely to be important issues for not only prediction of follow-up recurrence, but also for selection of the

Table 2
Multivariate analysis of factors related to recurrence.

	Coefficient	SE	OR	95% CI	P value
Dome size (mm)	0.36	0.19	1.4	0.99–2.1	0.06
Neck width (mm)	0.48	0.29	1.6	0.91–2.9	0.10
Pcom diameter (mm)	1.0	0.44	3.0	1.3–7.1	0.01

SE: standard error, OR: odds ratio, CI: confidence interval.

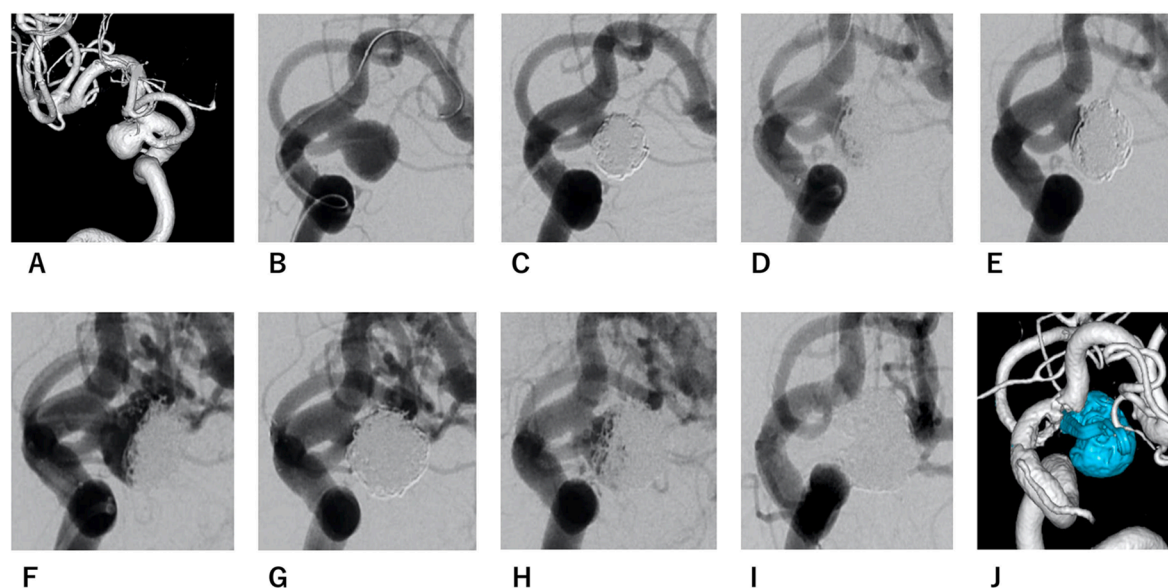


Fig. 2. Case of repeated recurrence after coil embolization for an IC-PC AN (A, B) 3DRA and working angle angiography showing the IC-PC AN before treatment, (C) angiography just after the first embolization, (D, E) angiography before and just after the second embolization, (F, G) angiography before and just after the third embolization, (H) angiography showing recurrence 9 months after the last embolization, and (I, J) working angle angiography and 3DRA 3 months after surgical clipping.

treatment modality (clipping or coiling). Further studies are required to confirm this finding of a relationship between Pcom diameter and recurrence.

This study has some limitations. First, it was a single-center study. Previous studies have shown that ruptured cases tend to recur after coil embolization, and the embolization results are related to recurrence [13,21]. Previous studies have shown that fetal type Pcom is an important factor related to recurrence as well, but the reason why the present result did not confirm it might be the small number of cases in this study. Second, the cases with difficult coil embolization (wide neck or tiny size) were prone to be treated by surgical clipping, so that such cases were excluded; thus, there might be a possibility of selection bias in this retrospective study. Third, the follow-up period was not very long. Some studies have found that the recurrence rate increases as the follow-up time is extended [7,13,22]; Raymond et al. in particular reported that cases followed up for <17 months were at lesser risk of recurrence than cases followed up for more than 17 months [23]. Longer follow-up might lead to an increased recurrence rate, so that the follow-up of the present patients needs to continue. Based on these issues, the present result needs to be confirmed in a prospective, large-scale study.

5. Conclusion

Dome size, neck width, aneurysm volume, and Pcom diameter were found to be related to recurrence after coil embolization for IC-PC ANs, and Pcom diameter in particular might be an independent risk factor. Examining these factors in combination could be useful for not only the prediction of follow-up recurrence, but also the selection of treatment modality.

CRediT authorship contribution statement

Shinya Fukuta: Conceptualization, Methodology, Investigation. **Chiyo Hikita:** Resources. **Mitsuhiro Iwasaki:** Resources. **Masahiro Maeda:** Resources. **Yasufumi Inaka:** Resources. **Hidekazu Yamazaki:** Resources. **Hiroaki Sato:** Resources. **Masafumi Morimoto:** Resources, Supervision. **Hidenori Oishi:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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