

Relationship between Focal Inflammation and Symptom Exacerbation after Endovascular Coil Embolization for Symptomatic Intracranial Aneurysms

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Key words: aneurysms, inflammation, coiling, complications

Summary

As endovascular surgery (EVS) of symptomatic unruptured aneurysms can result in symptom exacerbation due to intra-aneurysmal thrombosis or lump formation by coils, this treatment remains controversial.

We present five women ranging in age from 58 to 76 years (mean 65.6 years) who suffered post-EVS symptom exacerbation attributable to local inflammation.

The aneurysms measured from 8 to 25 mm (mean 19 mm) and were located at the cavernous portion in four patients and at the origin of the ophthalmic artery in one. All underwent endosaccular embolization under local anesthesia. Immediately after embolization, 24 h anti-coagulation therapy was started via the continuous injection of heparin; they also received anti-platelet therapy.

At one to three days post-EVS, all five patients manifested worsening of their cranial nerve symptoms.

In three other patients the symptoms were improved after EVS. We posit that inflammation induced by coil embolization may worsen cranial nerve symptoms transiently.

Our findings suggest that post-EVS follow-up is necessary and that patients exhibiting an inflammatory reaction be treated with anti-inflammatory drugs.

Introduction

Endovascular surgery (EVS) of symptomatic unruptured aneurysms exerting mass effect on the cranial nerves remains controversial¹⁻³. EVS can result in symptom exacerbation due to intra-aneurysmal thrombosis or mass effect by the coils. Elsewhere we reported the efficacy of EVS for symptomatic unruptured aneurysms⁴. To avoid symptom exacerbation, we insert coils tightly into the aneurysmal neck and less tightly on the dome side. We use anti-coagulation therapy to avoid thrombosis.

The immediate treatment outcome in some of our patients subjected to EVS was not favorable. Closer examination showed that their complications were related to post-EVS inflammation. To our knowledge, the relationship between EVS for intracranial aneurysms and local inflammation due to intra-aneurysmal thrombosis has not been documented previously. Here we report the occurrence of inflammation post-EVS for symptomatic intracranial aneurysms. We assessed the inflammatory reaction by counting the number of white blood cells (WBC) and by comparing the level of hypersensitive C-reactive protein (hs-CRP) before and one and seven days after the operation. We used these data to evaluate the relationship between postoperative symptom exacerbation and inflammatory reaction.

Material and Methods

Between April 1992 and April 2007 we treated 26 patients with unruptured internal carotid artery (ICA) aneurysms with cranial nerve palsy. Here we retrospectively evaluated five patients whose symptoms worsened after EVS. All were women aged from 58 to 76 years (mean 65.6 years). The aneurysms were located at the cavernous portion of the ICA in four patients and at the origin of the ophthalmic artery in one. The lesions measured from 8 to 25 mm (mean 19 mm). Details on the five patients are summarized in the table.

All embolization procedures were performed under local anesthesia. All patients received a systemic infusion of heparin with a bolus of 2000 U, followed by the continuous injection of 200 U/min. The activated coagulation time (ACT) was maintained at more than twice the control value. A microcatheter was carefully inserted into the aneurysm over a guide wire and the aneurysms were embolized with detachable coils. To avoid post-EVS symptom exacerbation, the coils were inserted tightly into the aneurysmal neck and more loosely into the dome. Appropriate embolization was confirmed angiographically and the procedure was finished. Post-embolization we delivered anticoagulation therapy via the 24 h continuous infusion of heparin; anti-platelet therapy consist-

ed of the oral administration of aspirin and ticlopidine.

We evaluated post-EVS cranial nerve symptoms and signs. All patients were followed by magnetic resonance (MR) angiography and thin-slice MR imaging. To assess the inflammatory reaction we counted the number of WBC and compared the hs-CRP levels before and one and seven days after the operation. To evaluate the relationship between post-EVS symptom changes and inflammatory reaction we compared data obtained on five patients with and three patients without post-EVS symptom exacerbation.

Results

We performed endosaccular embolization in four patients, the other patient underwent parent artery occlusion. Complete occlusion was achieved in two patients; in three there was a neck remnant. All five patients suffered post-treatment worsening of their cranial nerve symptoms; two patients each reported exacerbated optic nerve, oculomotor nerve, and abducens palsy. Worsening of the symptoms occurred at one to three days after the EVS procedure. Symptom improvement was achieved in three patients.

Before EVS, the mean number of WBC and the mean hs-CRP level was 5,400/ μ L (range 4,600-7,000/ μ L) and 140 μ g/dL (range 46-364 μ g/dL), respectively. One and seven days post-EVS these values were 8,860/ μ L (range 7,100-10,600/ μ L) and 6,660/ μ L (range 520-7,600/ μ L), and 1,678 μ g/dL (range 220-4,600 μ g/dL) and 430 μ g/dL (range 30-1,443 μ g/dL), respectively. These findings indicate marked post-EVS inflammatory reaction. In three other patients without post-EVS symptom exacerbation the mean number of WBC before and one and seven days after EVS was 5,833/ μ L (range 5,200-6,200/ μ L), 6,766/ μ L (range 6,100-6,766/ μ L), and 8,633/ μ L (range 6,200-10,400/ μ L); the mean level of hs-CRP was 58 μ g/dL (range 36-100 μ g/dL), 113 μ g/dL (range 53-221 μ g/dL), and 67 μ g/dL (range 30-139 μ g/dL).

As shown in figure 1A,B, post-EVS, the five patients with symptom exacerbation manifested a greater degree of inflammatory reaction than the patients without. After EVS, the body temperature of the five patients rose by range 0.8-3.0°C. One patient manifested an increase in the number of eosinocytes.

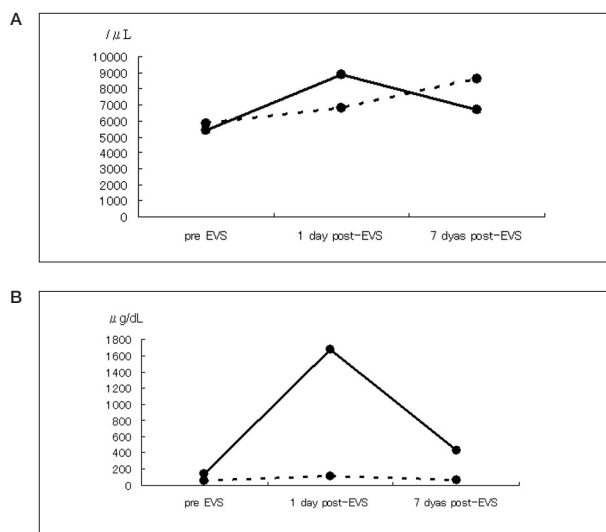


Figure 1 Post-EVS inflammatory reaction as determined by the number of WBC (A) and the hs-CRP level (B) in five patients with and three patients without symptom exacerbation. Solid line: patients without exacerbation; dotted line: patients with exacerbation

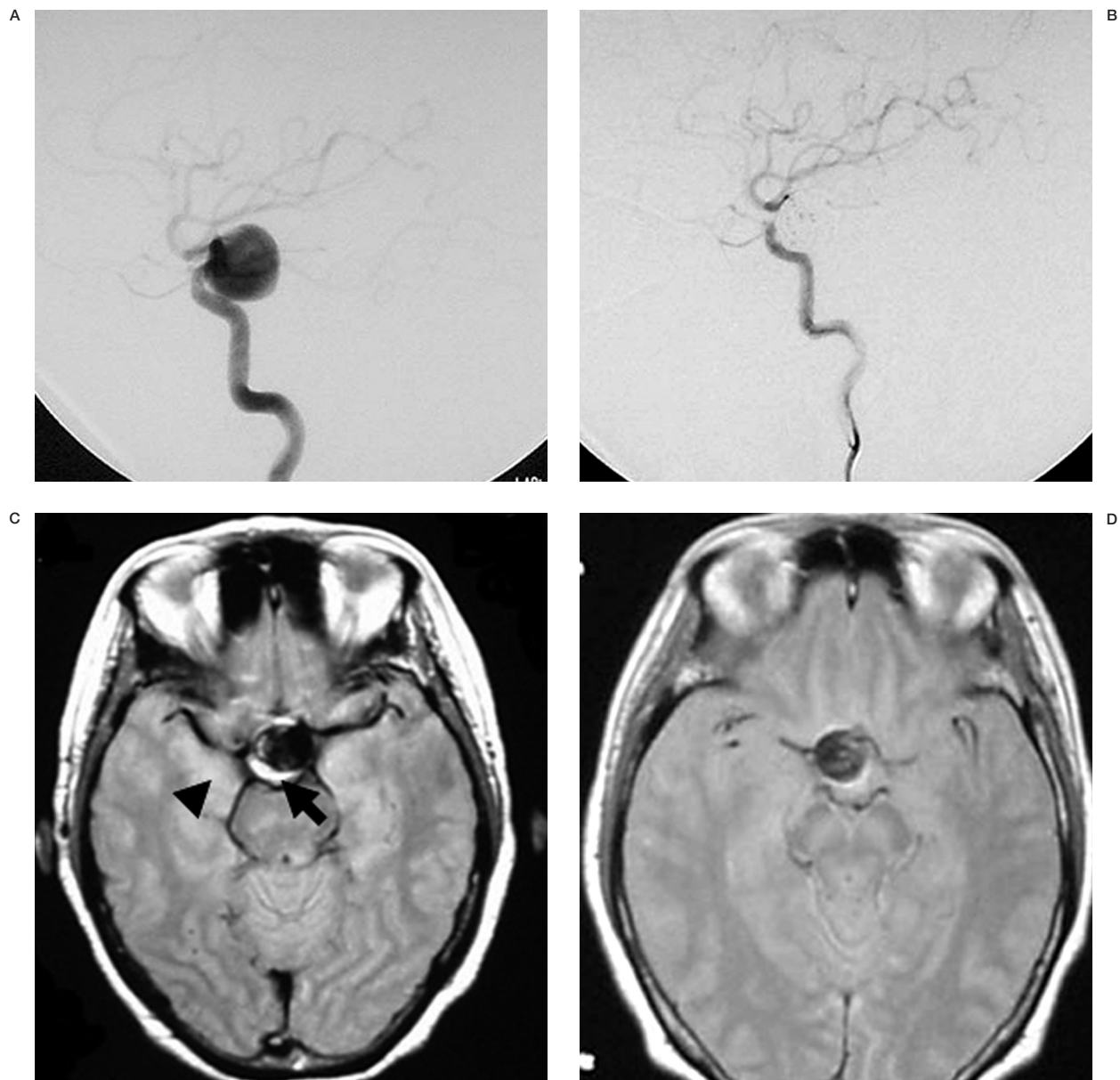


Figure 2 A) Pre-embolization angiograph showing a large intracranial aneurysm at the left internal carotid artery. B) Post-embolization angiograph showing inflow into the aneurysm via a neck remnant. C) MR images obtained 7 days post-EVS showing intra-aneurysmal thrombosis (arrow) and brain edema around the aneurysm (arrowhead). D) MR images obtained two years post-EVS showing disappearance of intra-aneurysmal thrombosis.

Case Presentation

Case 1

This 58-year-old woman had a four month history of progressive visual impairment. At admission she manifested pollinosis. MRI showed an aneurysm in the cavernous portion of the ICA. Angiography demonstrated that it was 17 mm in diameter (figure 2A). She was started on

anti-platelet drugs and underwent EVS under local anesthesia. At the start of the procedure she received a heparin bolus of 2,000 U; during the procedure we infused heparin systemically (200 U/min). Her activated coagulation time (ACT) was maintained at more than twice the control value. EVS was via the right femoral artery using an ENVOY guiding catheter (6-Fr; Cordis/ Johnson & Johnson, Miami, FL, USA).

An Excelsior 1018 microcatheter (Boston Scientific, Natick, MA, USA) was introduced into the aneurysm over the guide wire and the aneurysm was embolized using 18 Guglielmi detachable coils (GDC; Boston Scientific). A post-embolization angiogram showed inflow into the aneurysm via a neck remnant (figure 2B). Systemic heparin infusion was continued during the first 24h after EVS.

One day post-EVS her left visual acuity used by Landolt ring decreased from 0.07 to 0.06, her temperature was 38°C, her WBC rose from 5,300 to 10,600/ μ L, and her hs-CRP level from 98 to 220 μ g/dL. Steroid administration led to fever alleviation and her WBC and hs-CRP fell to 7,600/ μ L and 31 μ g/dL, respectively, by the seventh post-EVS day. At that time her left eyesight was 0.04. Post-EVS MRI disclosed intra-aneurysmal thrombosis (figure 2C) and brain edema around the aneurysmal site (figure 2C). On MRI scans obtained years later there was no evidence of intra-aneurysmal thrombosis (figure 2D) and her left visual acuity was 0.1.

Case 2

At a clinical survey, this 60-year-old woman was found to have a decrease in her bilateral eyesight and a homonymous quadrantic hemianopia. MRI performed at admission showed an aneurysm at the ophthalmic portion of the ICA. There was no history of allergic disease. Angiography demonstrated an aneurysm measuring 25 mm in diameter at the ophthalmic portion of the ICA (figure 3A). She was started on anti-platelet drugs and underwent EVS under local anesthesia. After the delivery of a 2,000 U bolus, she received a continuous infu-

sion of 200 U/min heparin. Her ACT was maintained at more than twice the control value. EVS was via the right femoral artery using an ENVOY guiding catheter (6-Fr; Cordis/Johnson & Johnson). An Excelsior 1018 microcatheter (Boston Scientific, Natick, Massachusetts, USA) was introduced into the aneurysm over the guide wire and the aneurysm was embolized using 22 GDC (Boston Scientific) and TRUFILL detachable coils (Cordis/Johnson & Johnson). A post-embolization angiogram showed inflow into the aneurysm via a neck remnant (figure 3B). We continued the systemic infusion of heparin during the first 24 h after EVS.

Two days after EVS her right and left visual acuity used by Landolt ring decreased from 1.0 to 0.7 and from 0.8 to 0.5, respectively and the homonymous quadrantic hemianopia increased to 1/2. Her temperature was 38°C, her WBC rose from 7,000 to 7,900/ μ L and her hs-CRP from 35 to 645 μ g/dL. The administration of heparin and steroids resulted in fever alleviation and a decrease in the WBC and hs-CRP level to 7,400/ μ L and 37 μ g/dL, respectively, at ten days post-EVS. Her bilateral eyesight was 0.3 at that time. Post-EVS MRI showed intra-aneurysmal thrombosis (figure 3C). At three months post-EVS her left and right visual acuity was 0.9 and 0.01, respectively. Her visual field defect did not improve.

Discussion

The cranial nerve symptoms in patients with unruptured intracranial aneurysms are due to mass effect or water hammer injury by pulsatile motion. The purpose of treatment is to remove

Table Summary of five patients with post-EVS symptom exacerbation.

Case	Age/ Sex	Location of An	Size of An (mm)	EVS	Result of EVS	Final CNS	Timing of CNS worse (day)
1	58F	RT IC cavernius	17	ESE	Neck remnant	Improvement	post EVS 3
2	60F	RT IC-Ophthalmic	25	ESE	Neck remnant	No change	2
3	74F	LT IC cavernius	8	ESE	Neck remnant	Improvement	2
4	76F	RT IC cavernius	25	PAO	Complete	No change	2
5	60F	RT IC cavernius	20	ESE	Complete	Improvement	1

EVS: endovascular surgery, ESE: endosaccular embolization, PAO: parent artery occlusion, CNS: cranial nerve symptoms

the mechanical pressure the aneurysm exerts on the cranial nerves and to stop its pulsation. Although aneurysmal clipping serves this purpose, it may be complicated by morphological or anatomical factors. Therefore, EVS is now an accepted modality to treat intracranial aneurysms.

Although EVS effectively addresses symptomatic unruptured intracranial aneurysms, this treatment remains controversial because it may result in symptom exacerbation due to intra-aneurysmal thrombosis or mass effect attributable to the inserted coils. On the other hand, unlike clipping surgery, EVS avoids direct iatrogenic injury to the brain. Elsewhere we reported the efficacy of EVS for symptomatic unruptured aneurysms⁴: cranial nerve symptoms were completely resolved in 46% of our patients and 33% manifested some improvement.

Stiver et al⁵ reported intra-aneurysmal changes after endosaccular embolization. Initially, inflammatory cells migrate into the aneurysm wall and later the center of the aneurysm contains organized fibrous tissue with newly formed capillaries. They encountered no whole-body inflammation attributable to uncoated coils. Guglielmi et al⁶ and Suzuki et al⁷ examined the efficacy of electrical thrombosis using uncoated coils. In experimental aneurysm models, Dawson et al⁸ and Murayama et al⁹ used collagen-coated platinum- and Matrix coils to elicit a local inflammatory reaction to increase the aneurysmal occlusion rate. However, the results were not satisfactory. The reaction elicited by uncoated platinum and tungsten coils was found to be different¹⁰.

The five patients presented here suffered post-EVS symptom exacerbation due to acute intra-aneurysmal thrombosis and manifested increased WBC and hs-CRP levels one day post-embolization. As expected, the embolization elicited an inflammatory reaction in the aneurysm and in tissue around the aneurysm. Allergic reactions to the inserted coils and intra-aneurysmal thrombosis due to local blood coagulation may be causative factors in patients exhibiting strong inflammatory reactions post-EVS. According to Takahashi et al¹¹ the lymphocyte transformation test is more useful than the patch test to assess allergies to nickel, cobalt, palladium, gold, chromium, and mercury and although platinum coils are thought not to elicit strong allergic reactions, this issue needs further study.

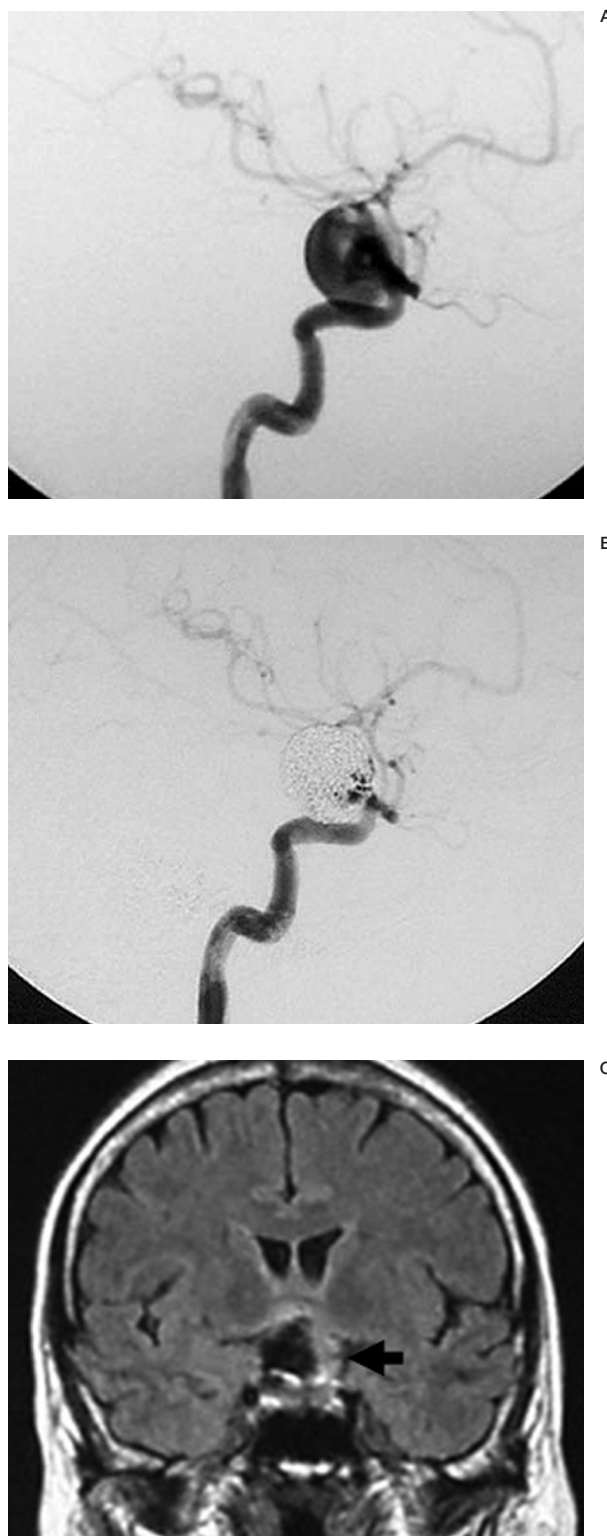


Figure 3 A) Pre embolization angiograph showing an internal carotid artery-ophthalmic artery aneurysm. B) Post-EVS angiograph showing inflow into the aneurysm via the neck remnant. C) MR images obtained 10 days post-EVS showing intra-aneurysmal thrombosis (arrow).

Kang et Al¹² studied hs-CRP as a marker of inflammation and reported a relationship between hs-CRP levels and the degree of vascular atherosclerosis. Based on our findings we suggest that patients with increased hs-CRP levels post-EVS require the administration of anti-inflammatory drugs, e.g. steroids, and anti-allergic drugs in addition to anti-coagulation drugs.

Conclusions

As the inflammatory reaction elicited by aneurysmal coil embolization may result in the exacerbation of cranial nerve symptoms due to aneurysmal mass effect, patients treated by EVS require the administration of anti-inflammatory drugs in addition to anti-coagulants.

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