A Case Report of Re-occlusion after Mechanical Thrombectomy to the Patient with Protein C Deficiency-associated Cerebral Infarction

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Objective: We encountered the case of re-occlusion occurred within a short time after thrombectomy to the patient with acute cerebral embolism complicated by protein C deficiency. We have reported this case as its clinical presentation is rare and important for considering a treatment strategy for young adult-onset cerebral embolism in the future.

Case Presentation: A 34-year-old male developed dysarthria, aphasia, and right hemiparesis and was diagnosed with cerebral infarction caused by left M1 occlusion. Mechanical thrombectomy was performed and achieved recanalization, but the same region was re-occluded after 7 hours and thrombectomy was repeated. The patient was diagnosed with protein C deficiency based on the blood test findings. Re-occlusion was considered due to epithelial damage by a stent retriever and a hypercoagulable state induced by protein C deficiency.

Conclusion: Since young adult-onset cerebral embolism may be complicated by underlying disease, such as coagulopathy like this patient, the possibility of re-obstruction induced by epithelial damage should be considered.

Keywords ▶ protein C deficiency, acute stroke thrombectomy, stent retriever, reperfusion catheters

Introduction

The efficacy and safety of thrombectomy for acute large vessel occlusion have been demonstrated by several randomized studies. We encountered a patient with protein C

deficiency-associated young adult-onset cerebral embolism treated with thrombectomy but the same artery was re-occluded within a short time and required retreatment. We have reported this case as it may offer valuable insight with regard to the treatment of protein C deficiency-associated cerebral embolism.

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Case Presentation

The patient was 34-year-old male. His chief complaints were dysarthria and right hemiparesis. Past medical history was none in particular, but his father developed cerebral infarction at 45 years old and had right hemiparesis and aphasia as sequelae.

History of present illness is as follows: family noticed the patient developed dysarthria, aphasia, and right hemiparesis 10 hours after the last time he was confirmed as healthy, and he was transported to our department 58 minutes after detection.

Physical findings are as follows: the height was 167 cm; body weight, 64.8 kg; blood pressure, 114/63 mmHg; heart rate, 50 bpm, regular; body temperature, 36.8°C; Glasgow

Fig. 1 On admission. (A and D) Non-contrast head CT. Low densities were noted in the left putamen and left caudate nucleus (white arrow). (B and E) Images of cerebral blood flow on head perfusion CT. Reduction was noted in the left insular cortex and lateral side of the left temporal lobe. (C and F) Images of mean transit time on head perfusion CT. Prolongation of the perfusion time was noted in the left MCA region. MCA: middle cerebral artery

Coma Scale (GCS), E4V3M6. On neurological examination, motor aphasia and right paresis were noted. The National Institute of Health Stroke Scale (NIHSS) score was 7.

Hematological findings are as follows: white blood cell, 9420/ μ L; C-reacted protein, 0.31 mg/dL; low-density lipoprotein cholesterol, 178 mg/dL; high-density lipoprotein cholesterol, 48 mg/dL; triglycerides, 83 mg/dL; hemoglobin A1c (HbA1c), 5.6%; prothrombin time-international normalized ratio, 1.03; activated partial thromboplastin time, 28 seconds; D-dimer, 0.44 μ g/mL; antithrombin III, 81%; thrombin-antithrombin III complex, 81%; thrombin-antithrombin complex, 4.4 ng/mL; brain natriuretic peptide, 35.3 pg/mL; antinuclear antibody, below 40 times; lupus anticoagulant, 1.16; anticardiolipin- β 2 glycoprotein I complex antibody, 1.2 U/mL or lower; protein C activity, 41% (normal range: 64–146); protein C antigen level, 39% (normal range: 70–150); free protein S antigen level, 89% (normal range: 60–150); protein induced by vitamin K absence-II (PIVKA II), 30 mAU/mL (normal range: below 40).

On head CT, no high density was detected, but early CT signs were noted in the left putamen and left caudate nucleus and the Alberta Stroke Program Early CT Score (ASPECTS) was 8 (**Fig. 1A** and **1D**). On head CTA, the

Fig. 2 Head CTA on admission. The left MCA M1 was occluded in the middle region (arrow). MCA: middle cerebral artery

left middle cerebral artery (MCA) M1 was obstructed in the middle region (**Fig. 2**). Regarding the mean transit time on head perfusion CT, the perfusion time prolonged in the left MCA region, but a decrease in the cerebral

Fig. 3 Percutaneous cerebral thrombectomy (1st). **(A)** Cerebral angiography before treatment. The left MCA M1 was occluded in the middle region (arrow). **(B)** Angiography through the Penumbra 3MAX reperfusion catheter before ADAPT. No occlusion was noted in the distal region. **(C)** Cerebral angiography after recanalization of the left MCA M1. The left MCA M2-3 was occluded (arrow). **(D)** Cerebral angiography at the end of the procedure. **(E)** Stenosis was noted in the proximal region of the left MCA M2 (arrowhead). ADAPT: direct aspiration first pass technique; MCA: middle cerebral artery; Penumbra 3MAX reperfusion catheter Penumbra, Alameda, CA, USA

blood flow was noted only in the left insular cortex and lateral side of the left temporal lobe (**Fig. 1B, 1C, 1E, and 1F**).

No left atrial enlargement or valvular disease was noted on transthoracic echocardiography performed after admission. On transesophageal echocardiography, no patent foramen ovale or intracardiac tumor was noted.

The patient was diagnosed with left M1 occlusion with an NIHSS score of 7 at 10 hours after the last time he was confirmed as healthy with an extensive mismatch between the ischemic core and ischemic region on head perfusion CT. Although RAPID software was not used, it was considered meeting the inclusion criteria of the DEFUSE3 trial, and mechanical thrombectomy was performed.¹⁾

Under local anesthesia, the right femoral artery was punctured, a 9Fr long sheath was placed, and a balloon guiding catheter, 9Fr Optimo (Tokai Medical Products, Aichi, Japan) was guided to the origin of the left internal carotid artery. Occlusion was detected at a site distal to the left M1 on angiography (**Fig. 3A**). Penumbra 5MAX ACE68 reperfusion catheter (Penumbra, Alameda, CA, USA) was navigated to the occluded region using Penumbra 3MAX reperfusion catheter (Penumbra) as an inner

catheter and CHIKAI 18-black (Asahi Intecc, Aichi, Japan) as micro guidewire. Clot aspiration was tried three times using the direct aspiration first pass technique (ADAPT),²⁾ but recanalization could not be acquired. Angiography was performed at this time and we confirmed there was no thrombus distal to the left MCA M2 inferior trunk was confirmed (**Fig. 3B**). Then, Marksman microcatheter (Medtronic, Minneapolis, MI, USA) was advanced to the left MCA M2 inferior trunk, and Trevo XP ProVue Retriever 3 mm × 20 mm (Stryker, Kalamazoo, MI, USA) was deployed in the left M1 over M2 (**Fig. 3C**). No thrombus was removed on the 1st time and a red thrombus was removed on the 2nd time, but the occlusion remained. When Penumbra 5MAX ACE68 was guided to the left internal carotid artery after about 15 minutes, left M1 recanalization and residual stenosis were noted. Thus, we determined that these findings indicated a spasm. On angiography, visualization of the M1 gradually improved and complete recanalization was confirmed, but the occlusion of left M2 inferior trunk was newly identified (**Fig. 3D**). It was considered that the left M1 developed spasm when the stent retriever was removed. For the occlusion of the left M2 inferior trunk, Penumbra 3MAX reperfusion

Fig. 4 Mechanical thrombectomy (2nd). (A) Cerebral angiography before treatment. Occlusion was noted in almost the same region as the 1st occlusion (arrowhead). (B) Cerebral angiography after recanalization of the left MCA M1. The left MCA M2 inferior trunk was occluded (arrow). (C) Cerebral angiography at the end of the procedure (arrowhead). MCA: middle cerebral artery

catheter was guided to the site, a red thrombus was removed using ADAPT, but the occlusion in this region remained. After waiting for 15 minutes, blood flow gradually improved, based on which it was considered that spasm occurred again, and 4 mg of nicardipine was administered locally via intra-arterial injection, by which complete recanalization of the occlusion of the left M2 inferior trunk was achieved. Stenosis was noted in a part of the left M2 superior trunk but it did not aggravate, and treatment so we finished the procedure at thrombolysis in cerebral infarction (TICI) grade 2b (**Fig. 3E**). The neurologic manifestation did not change from that before treatment and the NIHSS score was 7. Since hemorrhagic changes were noted on head CT immediately after treatment, no postoperative antithrombotic therapy was performed. The pathological finding of the removed thrombus was a fresh, mixed thrombus mainly comprised of fibrin and platelets mixed with neutrophils, but there was no endothelial cells. However, aphasia and right hemiplegia aggravated 7 hours after the 1st recanalization therapy and the NIHSS score was worsened to 15. Since re-occlusion was noted in almost the same region of the left M1 on MRI, percutaneous cerebral thrombectomy was repeated (**Fig. 4A**). Recanalization of the left M1 occlusion was achieved using the Penumbra 5MAX ACE68 reperfusion catheter and then recanalization of the residual left M2 occlusion was achieved using the Penumbra 3MAX reperfusion catheter (**Fig. 4B**). Stenosis was noted at the origin of the left M2, but it improved in the course observation and then reperfusion of TICI grade 2b was observed (**Fig. 4C**). The neurologic manifestations gradually improved thereafter and only mild aphasia remained on the 22nd hospital day, achieving

Fig. 5 Cerebral angiography on the 12th hospital day. Occlusion from the origin of the left M2 was noted (arrow).

an NIHSS score of 1. Residual left MCA stenosis was observed in the 2nd recanalization therapy, for which aspirin and cilostazol administration were initiated after the therapy. After protein C deficiency was diagnosed based on the blood test findings, aspirin was withdrawn and Warfarin administration was initiated. However, occlusion was noted at the origin of the left M2 on follow-up cerebral angiography performed on the 12th hospital day, and blood flow from the early bifurcation (anterior temporal branch) of M1 was noted (**Fig. 5**). The patient was transferred to a convalescence rehabilitation hospital on the 24th hospital day.

When protein C activity and antigen were examined in the patient's parents after protein C deficiency was identified in the patient, these were within the normal ranges in the father but the mother had protein C deficiency and the disease may be latent.

Discussion

Among congenital coagulation disorder, the incidence of protein C deficiency is relatively high, similar to those of protein S deficiency and antithrombin deficiency. Protein C deficiency induces a hypercoagulable state and causes deep venous thrombosis, pulmonary embolism, and mesenteric venous thrombosis.³⁾ It has also been pointed out as a risk factor for arterial thrombosis including myocardial and cerebral infarctions. In this case, he developed acute large vessel occlusion and was transported to our department, and protein C deficiency was identified by blood testing after admission. He had no atrial fibrillation was detected on Holter electrocardiography or monitoring, no carotid arterial stenosis, deep venous thrombosis, or patent foramen ovale. Following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, he may be classified as other causes of cerebral infarction, such as coagulopathy.

Mechanical thrombectomy performed to treat protein C deficiency-associated acute large vessel occlusion has not previously been reported, and there is only one case of protein S deficiency-associated acute large vessel occlusion treated with mechanical thrombectomy.⁴⁾ Regarding protein C deficiency, re-occlusion occurred during or after endovascular treatment have been occasionally reported⁵⁾ while some cases in which endovascular treatment was performed for occlusion of other blood vessels, such as pulmonary embolism⁶⁾ or lower limb vein,⁷⁾ and favorable reperfusion was achieved have been reported. In this case, he developed cerebral infarction and his protein C activity level was lower than the lower limit of the standard of adults. His father also developed cerebral infarction, antiphospholipid antibody syndrome and malignant tumor were excluded. According to the diagnostic criteria of idiopathic thrombosis of the Japan Intractable Diseases Information Center, this case can be diagnosed as protein C deficiency.⁸⁾ Since reduction of not only protein C activity but also the protein C antigen level was noted, it can be classified as type I protein C deficiency.

The re-occlusion site which developed after thrombectomy was almost the same as residual stenotic in the 1st treatment. It suggests that the 1st occlusion was due to embolism but the 2nd occlusion was caused by thrombotic occlusion due to vascular epithelial damage and the hypercoagulable state induced by protein C deficiency. Protein C is activated by modification of the thrombin function by thrombomodulin expressed on vascular endothelial cells and it inhibits unnecessary thrombus formation by inactivating Factors Va and VIIIa.^{7,9)} Thrombus formation may

have been promoted by impairment of vascular endothelial cells in the region with this impairment.

For the cause of vascular epithelial damage, we considered that it was mainly due to the stent retriever used in the 1st thrombectomy. Peschillo et al. compared vascular damage by thrombectomy for vascular occlusion between ADAPT and stent retriever in research using an animal model.¹⁰⁾ ADAPT caused slight degeneration of the tunica media and adventitia, whereas the stent retriever additionally caused denudation of the entire vascular epithelium and hypertrophy of the internal elastic membrane, strongly damaging the blood vessel. Therefore, when thrombectomy is performed to treat acute large vessel occlusion in cases suspected of having congenital coagulopathy, such as this case, ADAPT using a reperfusion catheter may cause less damage to the blood vessel and the risk for re-occlusion may be small compared with a stent retriever.

Although there is no consensus about the antithrombotic drug to be initially used as secondary prevention of young adult-onset cerebral infarction, even though the embolic source, such as atrial fibrillation and carotid artery dissection, is absent, anticoagulant therapy should be initiated in consideration of abnormal coagulation function, such as that performed in the present case.

Conclusion

We encountered a patient with young adult-onset cerebral infarction in whom protein C deficiency-associated large vessel occlusion was treated with mechanical thrombectomy and re-occlusion developed in the same region after thrombectomy. Young adult-onset cerebral embolism may be caused by congenital coagulopathy, and the possibility of endothelial damage-induced re-obstruction should be considered.

Disclosure Statement

None of the first and co-authors has conflict of interest.

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