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Case Report

A Case of an Early Pregnant Woman with Congenital Protein S Deficiency Who Underwent Mechanical Thrombectomy

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Objective: Large vessel occlusion (LVO) stroke during pregnancy is rare but a life-threatening issue for the mother and fetus. We report a rare case of a pregnant woman with congenital protein S deficiency who underwent mechanical thrombectomy.

Case Presentation: A 35-year-old woman presented with right hemiplegia and aphasia. The National Institutes of Health Stroke Scale was 23 and MRI revealed acute infarction on the left hemisphere. MRA showed disruption of the left middle cerebral artery. Mechanical thrombectomy was performed following intravenous thrombolysis, and then complete recanalization was achieved. The reduction in protein S activity due to pregnancy was suspected to have affected LVO. Subsequently, the patient was diagnosed with congenital protein S deficiency and recovered to modified Rankin scale 2 at 3 months after the onset.

Conclusion: Aggravation of congenital protein S deficiency due to pregnancy led to the onset of LVO. The patient showed a good outcome after mechanical thrombectomy.

Keywords ▶ stroke, thrombectomy, pregnancy, protein S, tissue plasminogen activator

Introduction

The incidence of stroke during pregnancy has been reported to be 30 in 100000, and the risk for cerebral infarction is about 3 times higher than that in healthy young people.[1)] In a nationwide survey of strokes in the US, ischemic stroke accounted for 71%, being high,[2)] but the incidence of stroke during pregnancy in Japan has been reported to be 10.2 in 100000 and ischemic stroke accounted for 25% of these.[3)] Congenital protein S deficiency is inherited thrombophilia with autosomal dominant inheritance caused by abnormality of the protein S gene (PROS1) gene, and the incidence is high in Japanese, being a risk factor of thromboembolism.[4)] We report a patient with congenital protein S deficiency, which aggravated with the progression of pregnancy and caused acute occlusion of the left middle cerebral artery. Mechanical thrombectomy was performed, and the outcome was favorable.

Case Presentation

Patient: A 35-year-old woman.
Medical history: None in particular. No past medical history of habitual abortion.
History of oral medication: No medical history of oral ontraceptive medication.
Familial history: None in particular.
Social history: Social drinker. No history of cigarette smoking.
Reproductive history: Gravida 4, para 3, and 1 abortion. No episode of thrombosis throughout pregnancy.
Present illness: Right hemiplegia and aphasia suddenly occurred in the patient, and she was transported to our hospital.
Findings on admission: Height 163 cm, body weight 55.9 kg, body mass index 21.04, blood pressure 103/60 mmHg, pulse 70/min (regular), body temperature 36.8°C, respiratory rate 23/min, and oxygen saturation 100%.

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Glasgow Coma Scale was 11. Severe right hemiplegia, right facial palsy, right conjugate deviation, and motor aphasia were noted, and the National Institutes of Health Stroke Scale (NIHSS) was 23.

Hematological findings: White blood cells 6200/μL, red blood cells 4340000/μL, platelets 261000/μL, C-reactive protein 0.01 mg/dL, low-density lipoprotein cholesterol 77 mg/dL, high-density lipoprotein cholesterol 56 mg/dL, triglycerides 37 mg/dL, hemoglobin A1c 5.5%, prothrombin time 11.8 seconds, prothrombin time international normalized ratio 1.00, activated partial thromboplastin time 27.2 seconds, fibrinogen 257 mg/dL (standard: 200–400 mg/dL), fibrin degradation products 10.2 μg (standard: 5 μg or lower), d-dimer 3.8 μg/mL (standard: 3 μg/mL or lower), antithrombin III 82.2% (standard: 80%–130%), thrombin–antithrombin (TAT) complex 6.0 ng/dL (standard: 3 ng/dL or lower), quantitation of rheumatoid factor <5.0 IU/mL, matrix metalloproteinase-3 30.8 ng/mL (standard: 17.3–59.7 ng/mL), anti-cardiolipin antibody 14 U/mL (standard: 10 U/mL or lower), protein C activity 87% (standard: 64%–135%), free protein S antigen level 26% (standard: 60%–127%), and homocysteine 6.6 nmol/mL (standard: 3.7–13.5 mg/dL).

Re-examination findings (7 days later): TAT complex 1.3 ng/dL, protein C activity 116%, free protein S antigen level 38%, protein S activity 20% (standard: 64%–149%), and protein S antigen level 63% (standard: 70%–140%).

Head CT: The corticomedullary junction had disappeared in the left temporal lobe cortex, and CT-Alberta stroke program early CT score (ASPECTS) was 8.

Head MRI: On diffusion-weighted image (DWI), a wide high-intensity region was noted in the left middle cerebral artery (MCA) region, being DWI-ASPECTS 3 (**Fig. 1A** and **1B**). On FLAIR, no change in the intensity was noted in this region. On MRA, visualization of the left distal MCA M1 region was disrupted (**Fig. 1C**).

The condition was diagnosed as juvenile-onset left M1 occlusion about 1 hour after the onset. Although DWI-ASPECTS was low, mechanical thrombectomy was performed immediately after intravenous thrombolysis with recombinant tissue plasminogen activator (t-PA). Under local anesthesia, the right femoral artery was punctured, a 9 Fr long sheath was placed, and a guiding catheter with balloon, 9 Fr Optimo (Tokai Medical Products, Aichi, Japan), was guided to the origin of the left internal carotid artery. The left carotid artery was imaged, and occlusion of the left MCA was observed in the distal M1 region (**Fig. 2A**). A Marksman microcatheter (Medtronic, Minneapolis, MN, USA) was guided to a site distal to the occluded region using a 0.014-inch Traxcess guidewire (MicroVention Terumo, Tustin, CA, USA), and Solitaire FR 4 × 20 mm (Medtronic) was deployed in the left M2 superior trunk over the left M1. When the stent retriever was retrieved, red thrombus was collected. Partial recanalization was observed, but occlusion of the superior trunk remained, for which a similar procedure was performed again and recanalization of thrombolysis in cerebral infarction (TICI) 3 was acquired by 2 passes (**Fig. 2B**). The onset to door was 32 minutes, door to puncture was 90 minutes, and door to recanalization was 110 minutes.

After treatment, moderate aphasia remained, but NIHSS was 5, showing marked improvement of symptoms. The patient had no history of arteriosclerotic disease, such as hypertension and dyslipidemia, and no preference for cigarette smoking. Based on blood test findings, protein S activity was declined, and the patient was in early pregnancy (5 weeks of gestation at the onset time of cerebral infarction) on abdominal ultrasonography. Anti-cardiolipin antibody was weakly positive, but the patient had no past medical history of habitual abortion, not applied to the diagnostic items, such as moderate or higher titer (>40 U/mL), and antiphospholipid syndrome was negative. In addition, the patient had no past medical history of skin symptoms, arthritis, cytopenia, or kidney disease, and complication by collagen disease, such as systemic lupus erythematosus, was also negative. On Holter electrocardiography, no arrhythmia causing cardiogenic embolism was observed, but an about 5-mm atrial septal defect was detected on transesophageal echocardiography. There was no right ventricular enlargement or pulmonary hypertension and no marked increase in pulmonary blood flow (Q_p/Q_s = 1.3), or the presence of a constant right-left shunt was confirmed. Valsalva maneuver was incomplete because examination was performed under sedation, so the presence of a right-left shunt during loading could not be excluded. No venous thrombus was detected on lower limb venous ultrasonography. No obviously active disease or malignant disease was detected on truncal CT.

The patient did not desire for childbearing, so the pregnancy was terminated, medication with oral warfarin was initiated as a secondary prevention, and the patient was transferred to a hospital for rehabilitation. The modified Rankin scale (mRS) was 2 (only moderate aphasia) at 3 months after the onset without recurrence of cerebral infarction.

Since the protein S antigen level and activity value had decreased on admission at which she was pregnant,

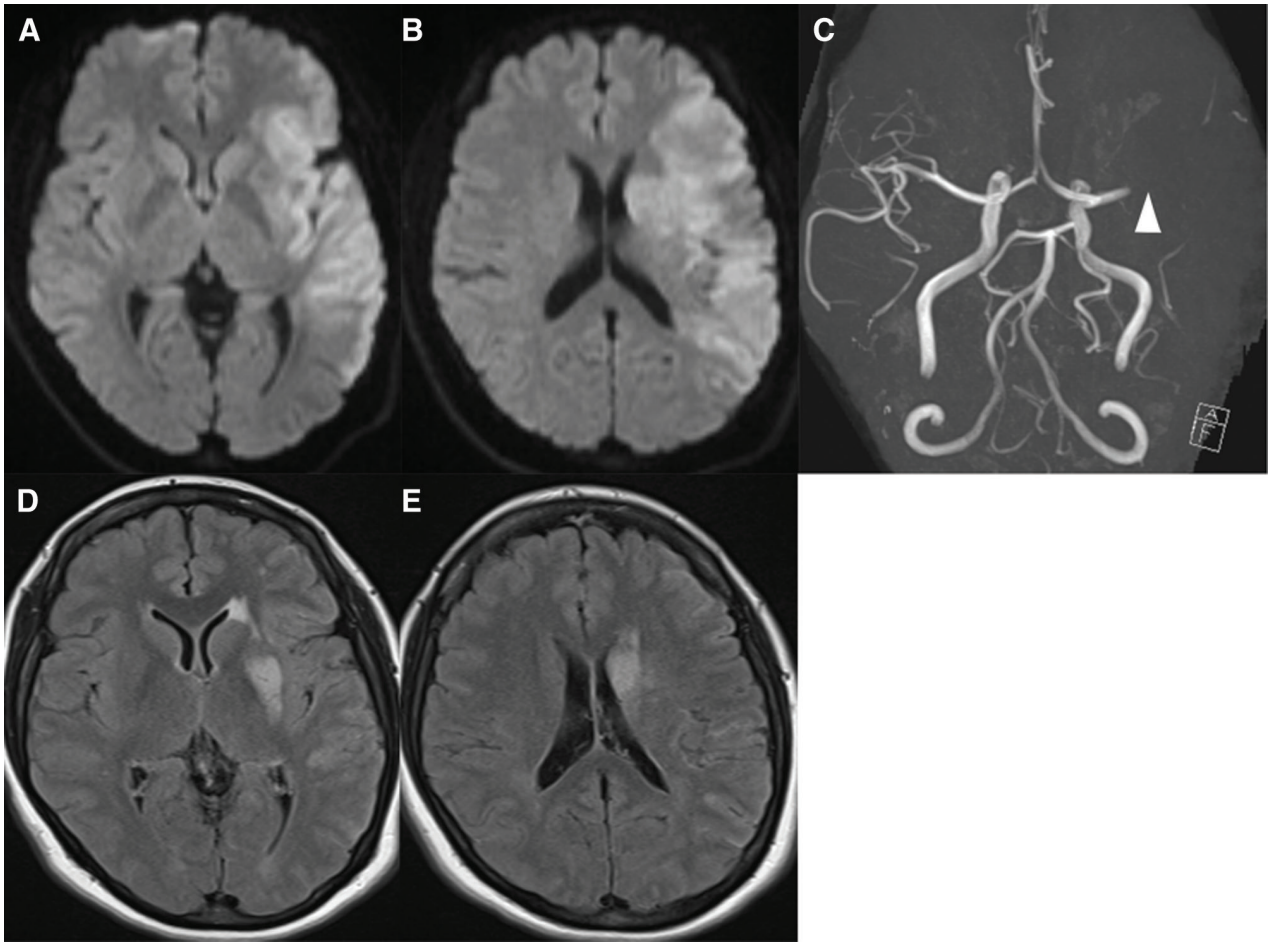

Fig. 1 (**A** and **B**) DWIs show acute stroke on the left hemisphere (DWI-ASPECTS is 3). (**C**) MRA shows disruption of the left middle cerebral artery at the M1 segment (white arrowhead). (**D** and **E**) FLAIR 2 days after the onset show the hyperintense area in part of the area of the left middle cerebral artery. ASPECTS: Alberta stroke program early CT score; DWI: diffusion-weighted image

secondary protein S deficiency accompanying pregnancy was presumed at the beginning after admission. However, close examination performed later clarified that both the protein S antigen level and the activity value decreased even after abortion and discontinuation of oral warfarin medication (**Fig. 3**). Since acquired protein S reduction was excluded and cerebral infarction developed in a young person, it was diagnosed as a congenital protein S deficiency.

Discussion

The efficacy of acute-phase treatment for large vessel occlusion (LVO) during pregnancy has not yet been clarified. In the guidelines established by the American Heart Association (AHA)/American Stroke Association (ASA), intravenous thrombolysis with t-PA is recommended when it is presumed that the benefit surpasses the risk. It is considered as having no sufficient evidence, and thrombectomy also has no sufficient evidence because pregnant women were excluded from the subjects of treatment in a large-scale clinical study.[5] However, the influence of radiation, contrast medium, and drugs, such as heparin, was very small and endovascular treatment could be performed in pregnant women relatively safely according to a report.[6] To our knowledge, there have been only 9 reports (19 patients) in which thrombectomy was performed for LVO in pregnant women[7–15] (**Table 1**). In the present patient, abortion was performed in response to the patient's request, but a favorable outcome was achieved in both mother and fetus in previous reports. In addition, Chalouhi et al retrospectively reported that the outcome of thrombectomy was favorable in young cerebral infarction patients.[16] Thrombectomy was performed in 55-year-old or younger patients with LVO and the outcome 90 days after treatment was

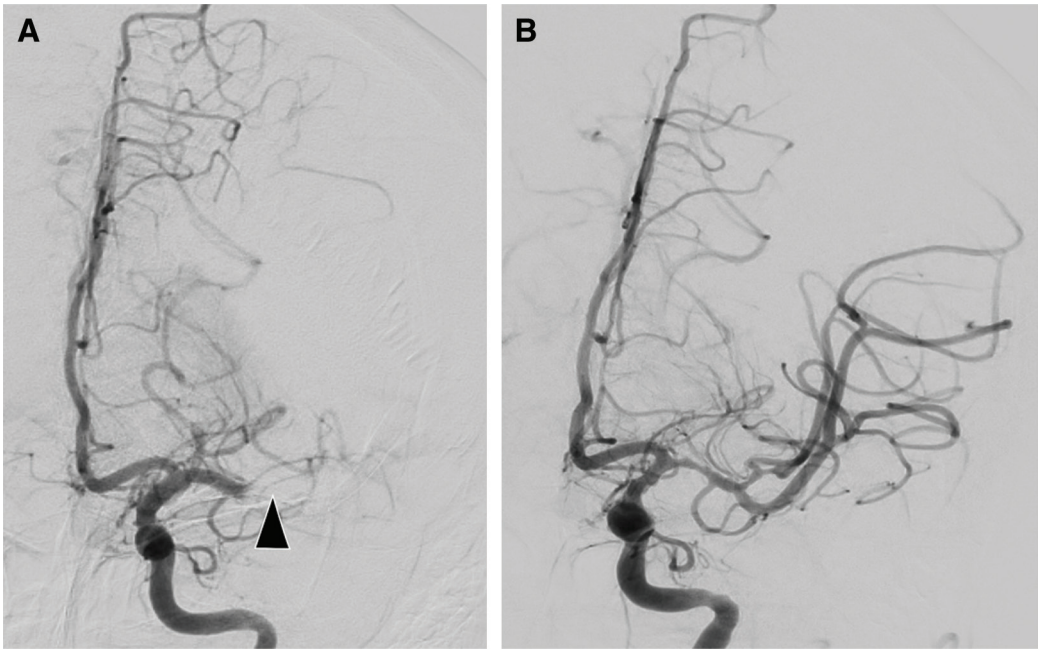

Fig. 2 (**A**) Left carotid angiogram shows occlusion of the left middle cerebral artery (black arrowhead). (**B**) Left carotid angiogram shows complete recanalization after the mechanical thrombectomy.

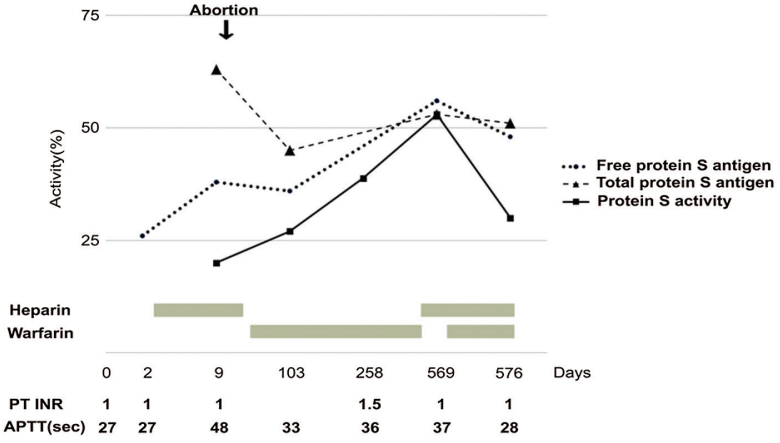

Fig. 3 The transition of free protein S antigen, total protein S antigen, and protein S activity during the course of treatment. APTT: activated partial thromboplastin time; PT–INR: prothrombin time international normalized ratio

favorable (mRS 0–2) in 77.5%, showing that the outcome is favorable compared with that in the elderly. They considered that the recanalization rate was high in young patients because arteriosclerotic change-induced tortuosity of vessels is scarce, resulting in a favorable outcome. Based on these findings, thrombectomy may be helpful for pregnant women who are young adults.

In a nationwide survey in Japan, reversible cerebral vasoconstriction syndrome, abnormal coagulation, cardiogenic embolus, atherothrombotic infarction, small vessel infarction, paradoxical embolus, arterial dissection, and moyamoya disease have been reported as a cause of cerebral infarction during pregnancy.[17] In the present patient, the presence of right-left shunt was not confirmed, but atrial septal defect was present and the defect hole was large, suggesting the presence of transient right–left shunt.

Protein S is a vitamin K-dependent coagulation-regulatory protein that inactivates factors Va and VIIa as protein C coenzyme and inhibits coagulation action.[4] About 40% of blood protein S is present as the free form and shows enzyme activity.[4] Protein S deficiency is a risk factor of deep vein thrombosis,[4] and it is considered a risk factor (odds ratio: 2.26, 95% confidence interval: 1.34–3.80) for cerebral infarction in a recent meta-analysis.[18] Congenital protein S deficiency is a hereditary disease with autosomal dominant inheritance, and it was included in designated

Table 1 Patient characteristics in published cases of mechanical thrombectomy during pregnancy in the literature

Case	References and year	Age	Gestational trimester (weeks)	Location	NIHSS	Intravenous t-PA	Complication	Final mRS	Fetal outcome	Etiology
1	Aaron et al., 2016[7]	24	Third	Right MCA	20	No	No	0	Healthy	Mitral valve replacement
2	Aaron et al., 2016[7]	28	Third (37)	Left MCA	21	No	No	2	Healthy	Mitral valve replacement
3	Bhogal et al., 2017[8]	38	Second (24)	Left MCA	15	No	No	2	Healthy	Drug abuse
4	Bhogal et al., 2017[8]	36	Second (25)	BA	N/A	Yes	No	1	Pregnancy on going	Ascending aorta reconstruction
5	Watanabe et al., 2019[9]	36	Third (36)	Left ICA	13	Yes	No	2	Healthy	Cryptogenic
6	Shah et al., 2018[10]	37	First (9)	Right MCA	9	Yes	No	1	Pregnancy on going	Cardiomyopathy
7	Zhu et al,. 2018[11]	28	First (9)	Left MCA	13	Yes	No	0	Healthy	N/A
8	Blythe et al., 2019[12]	29	Third (39)	Right MCA	11	Yes	No	0	Healthy	Factor XI deficiency
9	Szuchy et al., 2019[13]	26	Third (33)	Right MCA	14	Yes	Minor hemorrhage	2	Healthy	N/A
10	Tse et al., 2019[14]	28	Third (39)	Left MCA	11	N/A	No	1	Pregnancy on going	N/A
11	Tse et al., 2019[14]	27	Third (36)	Left MCA	22	N/A	No	0	Healthy	N/A
12	Tse et al., 2019[14]	36	First (8)	Left MCA	21	N/A	No	2	Healthy	Unknown
13	Limaye et al., 2020[15]	N/A	Second	Right MCA	15	Yes	No	1	Healthy	N/A
14	Limaye et al., 2020[15]	N/A	Second	Left MCA	18	No	No	2	N/A	N/A
15	Limaye et al., 2020[15]	N/A	First	Right MCA	11	Yes	Minor hemorrhage	1	Abortion	N/A
16	Limaye et al., 2020[15]	N/A	Third	Right ICA	12	No	No	0	Healthy	N/A
17	Limaye et al., 2020[15]	N/A	Third	Right MCA	12	Yes	No	1	Healthy	N/A
18	Limaye et al., 2020[15]	N/A	Third	Right MCA	28	No	No	0	Healthy	N/A
19	Limaye et al., 2020[15]	N/A	First	Left MCA	9	No	No	0	N/A	N/A
20	Present case	35	First (5)	Left MCA	23	Yes	No	2	Abortion	Protein S deficiency

ICA: internal cerebral artery; MCA: middle cerebral artery; mRS: modified Rankin scale; N/A: not applicable; NIHSS: National Institutes of Health Stroke Scale; t-PA: tissue plasminogen activator

intractable diseases in Japan in 2017. The cause is mutation of the PROS1 gene located at chromosome 3 q11.1 encoding protein S, and the frequency is high in Japanese, about 10 times higher than the frequency (1%–2% of population) in Western people.[4] It is definitely diagnosed by identification of genetic abnormality, but the detection rate of

PROS1 gene mutation is about 50%, being very low, so it is considered not essential for making a diagnosis. The important things for making a diagnosis are to observe clinical findings suggesting inheritance, such as repeated thrombosis, juvenile-onset (40 years old or younger), rare thrombosis development site, and the presence of a patient with similar symptoms in the family, and demonstration of reduced protein S activity in a state excluding elements of acquired development.[19] The subtype is determined based on the degrees of the total and free protein S antigen levels: Reduction of both levels is designated as type I, normal levels of both items is designated as type II, and reduction of the latter alone is designated as type III.[4] The protein S activity level varies depending on the age and sex, and it is known that the activity level decreases in pregnant women.[20–22] The total and free protein S levels decrease as pregnancy progresses, a significant decrease occurs in the second trimester of pregnancy, and the decrease prolongs.[20] Faught et al. reported that during pregnancy, the free protein S antigen level markedly decreased during 26–28 weeks of gestation compared with the level during 8–16 weeks of gestation, and the low level persisted during 36–38 weeks of gestation.[21] Basaran et al. measured free protein S in pregnant women, and it was 62.48%±19.58%, 53.36%±12.94%, and 44.61%±10.64% in the 1st, 2nd, and 3rd trimesters of pregnancy, respectively, showing that protein S activity declines with the progression of pregnancy.[22] In the perinatal period, the risk of onset of cerebral infarction is the highest in the 3rd trimester (28–40 weeks of gestation),[2] for which contribution of decreases in the protein S activity and free protein S antigen levels with pregnancy to the risk of onset of cerebral infarction is considered.[21] In addition, it has been reported that protein S clearly decreased from early pregnancy in patients with congenital protein S deficiency, being a problem.[20] In the present patient, decreases in the protein S activity and total and free protein S antigen levels were noted after excluding acquired elements and LVO developed, based on which congenital protein S deficiency Type I was diagnosed. In addition, the free protein S antigen level was abnormally low immediately after the onset of cerebral infarction that occurred in early pregnancy (**Fig. 3**), suggesting that congenital protein S deficiency aggravated upon pregnancy and paradoxical embolism onset through the atrial septal defect despite the time point being early pregnancy. To our knowledge, this is the first case in which thrombectomy was applied to congenital protein S deficiency-induced LVO stroke. However, for examination of cerebral infarction in the future, it may be necessary to take into consideration that congenital protein S deficiency is not a rare disease in Japanese and thromboembolism may develop due to aggravation of predisposition by acquired factors, such as pregnancy.

This patient had a favorable outcome despite a low DWI-ASPECTS of 3. A retrospective study in which patients with low ASPECTS were compared between those treated with thrombectomy and medical treatment has recently been reported. According to Campbell et al., although the outcome tended to become poor with an increase in the ischemic core volume, the outcome was more favorable in the thrombectomy group even though the ischemic core volume was extensive.[23] On multivariate analysis, the outcome was more favorable as the patient was younger and imaging to reperfusion was shorter. Applying thrombectomy should be considered in each patient when a short recanalization time can be expected even though ASPECTS is low in young patients.

Conclusion

LVO stroke caused by pregnancy-induced aggravation of congenital protein S deficiency was treated with mechanical thrombectomy and achieved a favorable outcome despite ASPECTS being low.

Disclosure Statement

The authors declare no conflicts of interest.

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