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Successful Thrombolysis and Mechanical Thrombectomy in an Early Pregnant Woman with Protein S Deficiency and Arterial Ischemic Stroke: A Case Report

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ABSTRACT

Protein S deficiency causing arterial ischemic stroke during pregnancy is uncommon. Delay or omission of treatment with perfusion therapies may worsen outcomes for both the mother and the fetus. In this paper, we report a case of an early pregnant woman with protein S deficiency and multiple history of chronic cerebrovascular disease who underwent successful thrombolysis and mechanical thrombectomy. The patient is a 35-year-old woman, eight weeks pregnant, with a history of protein S deficiency and chronic cerebrovascular disease, presenting with right-sided weakness and aphasia. Initial National Institutes of Health Stroke Scale was 10 with cranial magnetic resonance imaging findings of acute infarcts on the left caudate, lentiform nucleus, insula, and frontal lobe with a large vessel occlusion on the proximal M1 segment of the left middle cerebral artery. Intravenous thrombolysis and mechanical thrombectomy were performed with complete recanalization. The patient improved and delivered without any complications after 8 months. Protein S deficiency can contribute to arterial thrombosis including ischemic stroke. Arterial ischemic stroke and large vessel occlusion can cause significant disability if not treated appropriately. Reperfusion therapies in pregnant women show favorable outcomes and should be performed if the benefits outweigh the risks.

INTRODUCTION

Arterial ischemic stroke (AIS) is a severe but uncommon complication that can occur during pregnancy. Pregnancy increases the likelihood of cerebral infarction due to changes in hemodynamics and venous stasis, leading to a hypercoagulable state.[1] This hypercoagulability results from elevated procoagulants (factors VII, VIII, X, and fibrinogen) and reduced natural anticoagulants like protein C and protein S.[2] These proteins are vitamin K-dependent plasma glycoproteins involved in anticoagulation by inactivating factors Va and VIIIa.[3] Protein S activity reduces significantly during pregnancy by over 50%, especially in the first trimester, increasing the risk of thrombotic events at this time. While inherited thrombophilias such as protein S deficiency (PSD) are known to increase the risk for venous thromboembolism, their impact on arterial thrombosis, including conditions like AIS is still not fully understood.[4] Treating ischemic stroke during pregnancy is challenging due to concerns of fetal toxicity, especially in the first trimester when teratogenic risk is the highest. Delay or omission of treatment with perfusion therapies may worsen outcomes for both the mother and the fetus. In this report, we discussed the case of a 35-year-old female, at 8th week age of gestation, with known PSD, who presented with an arterial thrombotic

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event and underwent IV thrombolysis and mechanical thrombectomy.

Case

A 35-year-old female right-handed, primigravid, at 8th weeks age of gestation (AOG), with a history of PSD and chronic AIS on the left frontoparietal lobe (2017 and 2020) with modified Rankin Score (mRS) of 0 presented with sudden onset right-sided weakness and aphasia. She had no history of diabetes, hypertension, dyslipidemia, smoking, or contraceptive use. The patient was maintained on dabigatran 110mg/tab twice daily which was discontinued due to pregnancy and shifted to enoxaparin 0.4ml subcutaneously daily, then to tinzaparin 0.45ml subcutaneously daily after 3 days. Tinzaparin was continued until one day before ictus. The patient was brought to the emergency department within 3.5 hours of waking up. Her vital signs were stable: blood pressure 130/80mmHg, heart rate 100bpm sinus, respiratory rate 21cpm, afebrile, O2 saturation of 98% on room air, and random blood glucose of 111mg/dl. Her initial National Institute of Health stroke scale (NIHSS) was 10 – broca's aphasia with right-sided hemiparesis, with a manual muscle testing (MMT) score of 2/5. Laboratory tests such as complete blood count, electrolytes, liver enzymes, and bleeding parameters were normal. The 12L ECG and transthoracic echocardiogram were negative. Her lipid profile showed an elevated LDL level of 130mg/dL.

Previous workup for stroke in the young in 2017 and 2020 were not repeated including the transesophageal echocardiography which showed no patent foramen ovale. PSD had been confirmed based on three consecutive detections of low protein S level: 48%, 33%, and 50% in 2017, August 2018, and November 2018, respectively. Protein C was normal. Anti-cardiolipin IgM and IgG, beta 2 glycoprotein IgM and IgG, lupus anticoagulant, anti-dsDNA, anti-smith, anti-ribonucleoprotein,

Figure 1. Areas of restricted diffusion on the left caudate, lentiform, insula, and frontal lobe shown on diffused weighted imaging (DWI), with corresponding signal drop on apparent diffusion coefficient (ADC) without any fluid-attenuated inversion recovery (FLAIR) hyperintensities and absent susceptibilities on gradient recalled echo (GRE).

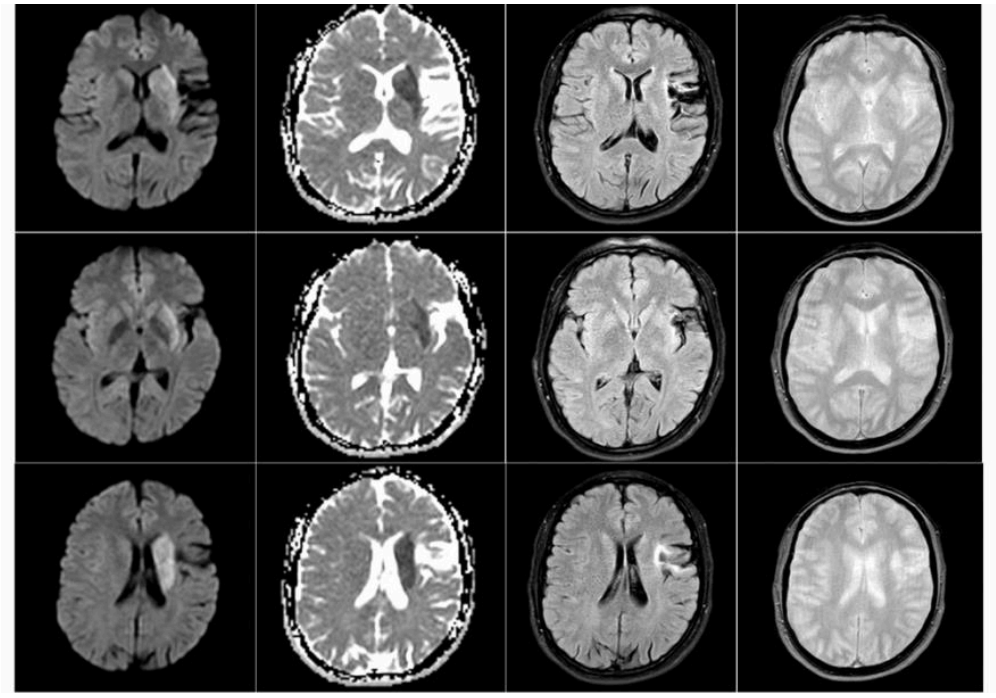


Figure 2. Cerebral angiography showing the A) occlusion of the M1 segment of the left MCA B) Complete recanalization after MT .

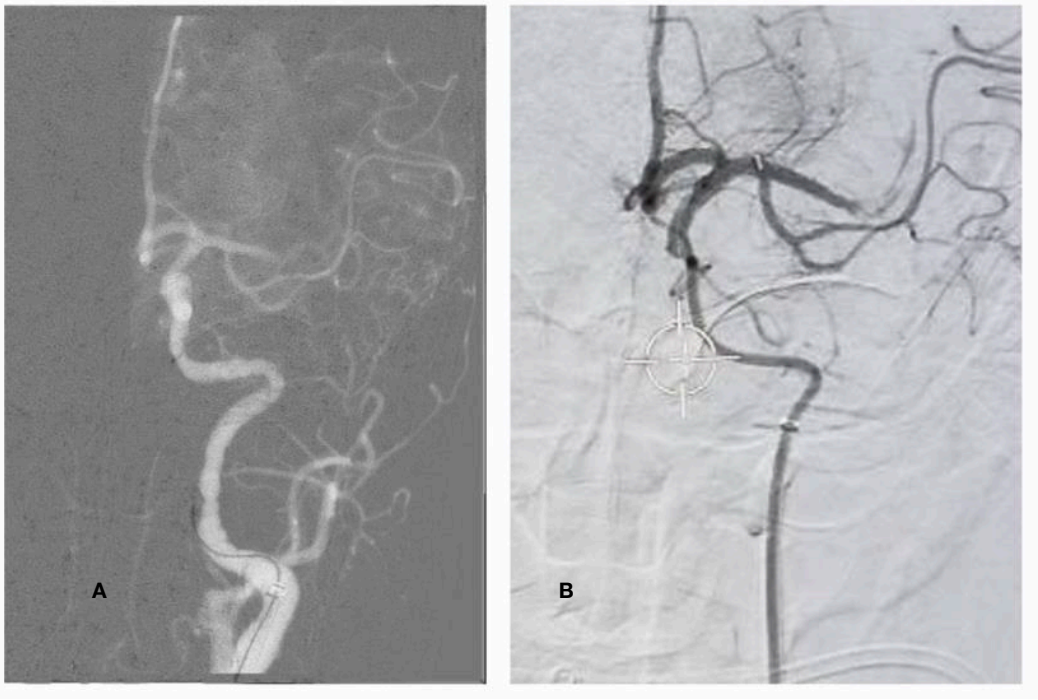
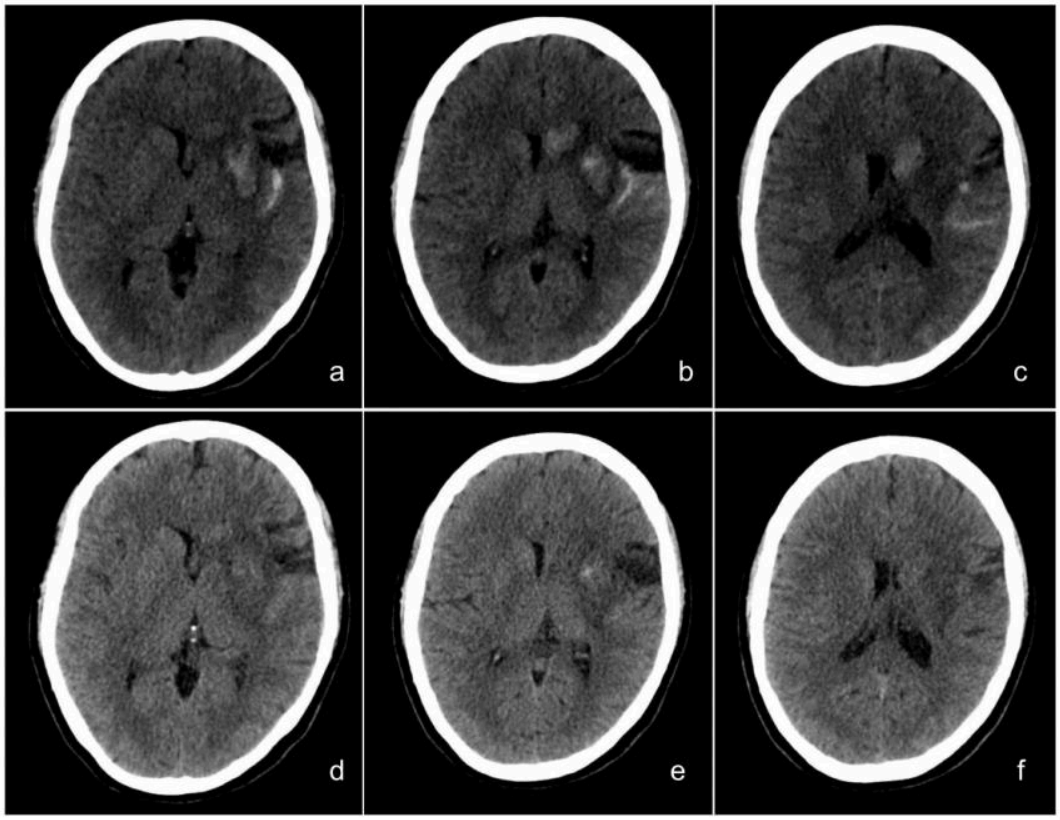


Figure 3. Images a-c: Cranial CT scan 1 day post rTPA and thrombectomy; images d-f: Cranial CT scan 7 days post rTPA and thrombectomy.



complement 3 and 4, factor V leiden and antithrombin III were all negative.

A non-contrast cranial magnetic resonance imaging (MRI) showed acute ischemic lesions on the left caudate, lentiform nucleus, insula, and frontal lobe, with no corresponding hyperintensity in fluid-attenuated inversion recovery (FLAIR) sequence (see Fig 1). Post-imaging, the NIHSS increased to 17 with global aphasia, right-sided severe sensory loss and hemiplegia. Alteplase was administered 2 hours and 5 minutes from ictus. The magnetic resonance angiogram (MRA) showed a large vessel occlusion in the proximal M1 segment of the left middle cerebral artery (MCA). The patient underwent mechanical thrombectomy (MT) with successful recanalization (mTICI score of 3) (see Fig 2) at 4 hours and 15 minutes from waking, and door to reperfusion time of 5 hours and 17 minutes.

The patient was admitted and was started on atorvastatin 10mg daily. A follow-up cranial CT scan was done 24 hours post-thrombectomy and showed a stable infarct with minimal hemorrhagic conversion (see Fig 3 a-c). The patient's NIHSS score improved to 8 with motor strength of the right lower extremity increasing to 4/5. On day 7 post-ictus, a surveillance cranial CT scan showed stable infarct with regression of the hemorrhagic conversion (see Fig 3 d-f) hence was started on a low molecular weight heparin (LMWH) 0.4ml subcutaneously twice daily.

She was discharged on day 12 with NIHSS score of 5, showing mild anomic aphasia, mild right-sided sensory deficit, and hemiparesis. At 16 weeks AOG, statin was discontinued. She was maintained on LMWH and started on aspirin for pre-eclampsia prevention. The fetus remained healthy and was delivered at 37 weeks and 1 day (day 204 from symptom onset) via cesarean section without any complications for the mother and the neonate. There were no apparent abnormalities observed in the newborn during the first 6 months of life. Anticoagulation was resumed on day 2 post delivery and the mother's MRS remained at 1.

DISCUSSION

Inherited thrombophilias such as PSD are known risk factors for venous thromboembolism, but their contribution to arterial thrombosis, including AIS is still unclear. Chiasakul et al. (2019) suggest that inherited thrombophilias may contribute to AIS through excessive thrombin activation which can lead to atherosclerosis by triggering platelet activation and endothelial and vascular cell dysregulation.[4] The protein S level is known to progressively decrease in pregnant women from the first through third trimester, increasing the risk of stroke at 28 to 40 weeks of gestation. In individuals with existing congenital protein S deficiency, this decline starts earlier.[5] Although genetic testing was not performed, the patient has consistently low protein S levels even before pregnancy, indicating congenital PSD. She also did not have any conditions linked to acquired PSD, such as infections, severe liver disease, systemic lupus erythematosus, or the use of oral contraceptives. Her protein S deficiency, worsened by pregnancy, likely contributed to the large vessel occlusion. The patient had been on dabigatran for three years without any recurrence of ischemic events. However, its discontinuation during pregnancy, along with suboptimal anticoagulation, increased her stroke risk. She had no other vascular risk factors or autoimmune conditions that could explain the ischemic event.

Intravenous thrombolysis using recombinant tissue plasminogen activator (IV rTPA) and endovascular mechanical thrombectomy (MT) are effective for AIS, but their safety during pregnancy remains uncertain, as pregnant women were excluded from major clinical trials.[7] The American Heart Association (AHA) considers pregnancy as a relative exclusion criterion for IV rt-PA, classified under category C. While IV rTPA

does not cross the placenta and its teratogenic effect has not been proven[9], maternal hemorrhagic complications have been reported in 8% of cases.[8] Overall, the risk of IV rtPA during pregnancy appears to be relatively low and is not deemed an absolute contraindication. The potential for severe disability if untreated should guide decision-making in pregnant stroke patients.

MT is also considered safe in pregnant women with minimal risk of radiation, contrast medium, and heparin.[9] Fetal radiation exposure in diagnostic stroke imaging and mechanical thrombectomy is comparable to or lower than emergency diagnostic imaging.[10] According to Ishii and Miyamoto[9], absorbed fetal radiation dose in a general endovascular procedure is approximately 2.8 mGy, significantly below the 100-200 mGy threshold for organogenesis disruption (2-8 weeks) and the 120 mGy threshold for mental retardation risk. Based on existing literature, there were 20 pregnant women diagnosed with large vessel occlusion with stroke scales ranging from 9 to 28 who underwent MT (9 out of the 20 were given intravenous thrombolysis before thrombectomy). Six cases occurred in the first trimester and none had serious complications. Functional outcomes were generally good (mRS 0-2), with 13 good fetal outcomes. Two chose abortion, and fetal outcomes were unreported for the remaining cases. Only 1 out of the 20 patients had protein S deficiency as the risk factor for the arterial event.[11] This data supports the relative safety of MT during pregnancy, especially in the absence of major complications and with good maternal and fetal outcomes.

Statins have anticoagulant effects and are found beneficial in hypercoagulable states. However, their use during pregnancy is limited due to category X classification based on reports of fetal outcomes. Statin use in the first trimester was not associated with an increased risk of congenital anomalies after accounting for confounding factors. It was however linked to a higher risk of preterm birth and low birth weight, particularly with prolonged exposure until the second and third trimesters.[12,13] Our patient received statin during the AIS which was discontinued during the 2nd trimester.

Continuous follow-up is crucial to monitor for both maternal and fetal outcomes. The patient had significant improvement in neurologic function and this emphasizes the importance of timely stroke recognition and reperfusion therapies for AIS in the pregnant population.

CONCLUSION

Protein S deficiency increases the risk of both venous thromboembolism and arterial thrombosis, including AIS. This risk is higher in pregnant women with congenital PSD, as the protein S levels decrease significantly in the early weeks of pregnancy. Acute ischemic stroke and large vessel occlusion can cause substantial disability if not managed appropriately. There is a high likelihood of favorable outcomes in a pregnant woman after IV thrombolysis and MT. Therefore, these reperfusion therapies should be performed if indicated and if the benefits outweigh the risks.

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