CASE REPORT

Favorable Feto-maternal Outcome in a Case of Chronic Deep Vein Thrombosis Patient due to Protein S Deficiency: A Case Report

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Abstract

Background: Protein S (PS) deficiency is an inherited thrombophilia and is inherited as autosomal dominant form. When it occurs in pregnancy, there may be adverse outcomes for both the mother and the fetus. Mother can have recurrent thromboembolic episodes and recurrent pregnancy loss (RPL), while baby can have fatal condition like purpura fulminans (PF) when it occurs in homozygous state.

Case description: We present to you a case of chronic deep vein thrombosis from the past 2 years which was diagnosed to be due to PS deficiency. While she was on oral anticoagulant thromboprophylaxis (Dabigatrin), she had conceived spontaneously. During her antenatal period, she was prescribed low molecular weight heparin thromboprophylaxis (Enoxaprin) throughout pregnancy. She underwent an emergency cesarean section and had a good pregnancy and fetal outcome.

Clinical significance: Anticoagulation therapy plays a vital role in achieving a successful pregnancy outcome in cases of inherited thrombophilias.

Keywords: Case report, Chronic deep vein thrombosis, Protein S deficiency, Thromboprophylaxis.

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Introduction

Protein S (PS) deficiency is a rare-inherited thrombophilia that increases the risk of venous thromboembolism (VTE) and recurrent fetal loss during pregnancy. It affects between 1 in 500 and 1 in 3,000 generally, but its incidence may increase as high as 2–12% in thrombophilic patients.[1] Protein S deficiency is more common than protein C (PC) deficiency in the general population and among VTE patients.[1,2] Purpura fulminans (PF) is a catastrophic and deadly thrombotic event that occurs in newborns with homozygous PS deficiency patients.[1] Pregnancy is a hypercoagulable state due to physiological changes that promote clotting to prevent excessive bleeding during childbirth. According to James et al., pregnant women had a 5–10 fold higher risk of venous thrombosis than non-pregnant women of equivalent age, with an absolute risk of 1–2 per 1,000 deliveries.[3]

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Case Description

In December 2020, a 23-year aged female presented to surgery outpatient department with symptoms and signs of acute deep vein thrombosis in her right lower limb which was involving right common femoral vein, superficial femoral vein, popliteal vein and minimal extension to Sepheno-femoral junction and external iliac vein. There was no evidence of thrombosis in left lower limb. There was no family history of deep vein thrombosis (DVT) in the family. The thrombophilia profile revealed a 39% protein-S deficit (normal range: 55–123%) (Table 1). Though antithrombin III levels were <80%, it is a known fact that the levels could be reduced when the thrombus is present. She was admitted and started on heparin infusion immediately according to her weight and titrated based on activated partial thromboplastin time (APTT) results. She was then overlapped with warfarin 5 mg once a day (after 5 days of heparin infusion), with alternate-day prothrombin time–international normalized ratio (PT-INR) levels trending upward. Weekly PT-INR was measured, and after one month of using warfarin 5 mg once a day, the dose was increased to warfarin 10 mg once a day. Later, she was switched to oral dabigatran 150 mg twice daily and monitored every two weeks for nine months. On dabigatran, the patient needed admission thrice for acute to chronic thrombotic episodes of her right lower limb, for which she was treated with heparin infusions.

Patient wanted to conceive. The couple underwent a detailed pre-conceptional counseling. She was advised on periconceptional folic acid supplementation, early antenatal registration with the need for thromboprophylaxis throughout pregnancy with low molecular weight heparin (LMWH) and about the autosomal dominant nature of protein S deficiency. She conceived spontaneously in November 2021 and registered at a private clinic at 9 weeks of gestation. In view of PS deficiency, the patient who was on dabigatran pre-conceptionally

Table 1: Investigations of patients during the first episode of acute venous thrombosis

Investigations	*Results*
Bleeding time (BT)	1.5 (1–6 minutes)
Clotting time (CT)	5.5 (5–10 minutes)
Anti cardiolipin antibody (ACA)	IgM–12, negative (<12.5)
	IgG–2.1, negative (<20)
Lupus anticoagulant (LA)	Not detected
Free protein S	39% (non-pregnant–55–123; 1st, 2nd, 3rd Trimester–upto 95%/68%/42%)
Protein C	93% (non-pregnant – 70–130; 1st, 2nd, 3rd Trimester–upto 121%/133%/135%)
Anti thrombin III	65% (80–120)
APTT	34.5 (34.3)
PT	15.4 (14.4)
INR	1.08

was changed over to LMWH (Injection Enoxaparin 40 mg twice daily). She was put on progesterone supplements. She visited our hospital at 17 weeks of gestational age. She was maintained at Injection enoxaparin 40 mg twice daily. Doppler of the right lower limb showed features of chronic deep vein thrombosis with partial recanalization of the veins. During the prenatal period, the patient's PT-INR and platelet counts were checked every 2 weeks. At 32 weeks, ultrasonography (USG) with doppler showed healthy interval growth with normal doppler flows.

At 36 weeks, the patient developed right lower limb pain and swelling and was admitted for a thorough evaluation. A complete blood count and coagulation profile were done, and doppler of the lower limbs showed features of chronic DVT of the right limb with partial recanalization of the deep veins, and left lower limb was normal. At 37 weeks, she spontaneously went into labor. Low molecular weight heparin was stopped immediately. A trial of labor for 24 hours was given, and later she underwent a cesarean section for non-progressive labor. A female child weighing 2.26 kg was born. The neonate's thrombophilic profile was found to be normal. The mother was restarted on an injection Enoxaparin 40 mg after 12 hours. On post-operative day 4, bilateral lower limb doppler was done again, which showed chronic DVT changes in the right lower limb, and a normal venous doppler study for the deep veins of the left lower limb. From post operative day 7, the patient was switched over to oral Dabigatran 150 mg twice daily. Post operatively, after 1 month patient again developed acute deep vein thrombosis of the other lower limb (left side), doppler showed acute thrombus of left lower limb, involving left common femoral and superficial femoral veins, left popliteal vein with chronic DVT of right lower limb. Patient was admitted and heparinized again for the acute event and later restarted on Dabigatran 150 mg twice daily. Patient is presently on regular follow-up and doing fine till date on oral dabigatran.

Discussion

Protein S and C are vitamin-K dependent plasma proteins that work together to maintain the coagulation system. These inactivate factor Va and VIIIa. Protein S controls thrombin generation and fibrinolysis through both activated protein C (APC) dependent and independent anticoagulant capabilities (Fig. 1). Protein S deficiency in pregnancy

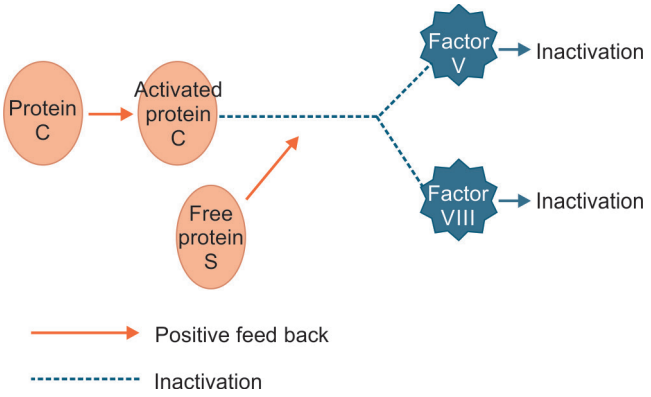

Fig.1: Role of Protein S in anticoagulation pathway

can lead to pulmonary thrombosis, placental hypoperfusion, fetal growth restriction, intra uterine death, miscarriage, recurrent pregnancy loss (RPL), microvascular thrombosis in placental blood vessels, pregnancy induced hypertension and abruption.[4] Free protein S levels fall in first and second trimester in pregnancy but doesn't decrease in third trimester.

Protein S is produced mostly in hepatocytes and also in osteoblasts, megakaryocytes, leydig, endothelial, and vascular smooth muscle cells. It circulates in plasma. Protein S deficiency is usually inherited, but some-times it can be acquired by several factors like vitamin-K antagonist medications, oral contraception, pregnancy, liver disease, nephritic syndrome, disseminated intravascular coagulation, and chronic infections. Individuals with a heterozygous deficiency of PS can present with a risk for DVT and RPL, whereas the homozygous state can have fatal neonatal consequences of PF.[5] Patients with PS deficiency can present with recurrent deep vein thrombosis, pulmonary embolism, or both, but rarely, it can involve superficial, cerebral, visceral, or axillary vein thrombosis too. The specific characteristics of PS and PS deficiency are described in (Table 2).[6]

Ming-Ching Shen et al. studied-on Taiwan population and found that LMWH improves the live birth rate in women suffering from RPL who have a verified single protein S deficiency.[7] Women who have inherited or acquired thrombophilia should take thromboprophylaxis during pregnancy and puerperium as they have an extremely high risk of developing prenatal and postpartum VTE.[8,9] The preferred anticoagulants are subcutaneous LMWH or unfractionated heparin. Heparin does not cause teratogenesis or fetal hemorrhage since it does not cross the placenta. Because it has less side effect (lower risk of osteopenia and thrombocytopenia), much safer for both the mother and the fetus, and once-daily dose for prophylaxis, LMWH is the recommended medication. A dose of 1 mg/kg of low molecular weight heparin (enoxaparin) was administered every 12 hours, starting on the day of enrollment and ending a few days (at least 24 hours) before birth.[7]

Dabigatrin is a newer direct thrombin inhibitor and is an alternative for heparin which can be used for thromboprophylaxis. Other alternatives like fondaparinaux (selective factor Xa inhibitor) and low dose aspirin have been used in pregnancy.[10]

In this case, the patient received LMWH throughout her pregnancy, which played a crucial role in achieving a successful outcome. In addition to anticoagulation therapy, regular fetal monitoring and ultrasound examinations were integral to managing this high-risk pregnancy. The interdisciplinary team, comprising hematologists,

Table 2: Main features of protein S and protein S deficiency

Gene name (location)	PROS1 or PS-alpha (3q11.2), more than 200 mutations have been identified
PS	Vitamin K-dependent plasma glycoprotein with 70,000Da; 60% bound, 40% free
Function PS	Cofactor to facilitate the action of APC on factor Va and VIIIa resulting in reduced thrombin formation
Clinical aspects of PS deficiency	VTE at young age (<30 years), unprovoked, at uncommon locations, recurrent, family history, recurrent fetal loss
Types of PS deficiency	Type I: Decreased APC cofactor activity, decreased total PS, decreased free PS (quantitative defect)
	Type II: Decreased APC cofactor activity, normal total PS, normal free PS (qualitative defect)
	Type III: Decreased APC cofactor activity, normal total PS, decreased free PS (quantitative defect)
	Type I and III account to 95% of the protein S deficiencies
Rule of 50	50% chance for men and women to be affected
	50% chance to pass it to their offspring (autosomal dominant)
	50% develop VTE by the age of 55 years
	50% of VTE is unprovoked

APC, activated protein C

obstetricians, and maternal-fetal medicine specialists, ensured that both maternal and fetal conditions were closely observed, allowing for timely interventions when necessary. The patient's compliance with therapy and regular follow-up visits were also important contributors to the excellent outcome. Throughout the pregnancy, education on the need for medication compliance and recognizing indicators of potential problems were emphasized. Antenatal care for thrombophilia should include case-based anticoagulant prophylaxis. Candidates for complete thromboprophylaxis include those who have experienced thromboembolic episodes in the past, who have very low PS activity, or who have experienced prior fetal losses that may have been caused by thrombophilia.[11]

Conclusion

Thrombophilia screening may be recommended for women with unprovoked personal thrombosis, a family history of thrombosis, and with RPL. Effective and suitable thromboprophylaxis is an important aspect of therapy for pregnant women with inherited thrombophilias for better obstetric and neonatal outcomes. Adequate measures should be considered in the antenatal, postpartum or postoperative periods to prevent pulmonary thromboembolism, which could lead to major maternal and fetal morbidity and mortality.

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