Protein S Deficiency in a Patient with Bad Obstetric History

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ABSTRACT

Protein S deficiency is uncommon. It may cause recurrent thrombosis and may complicate pregnancy. A patient with protein S deficiency presented with bad obstetric history of two blighted ovum and then had a successful pregnancy, managed with anticoagulation and close fetal monitoring. Anticoagulation therapy is the cornerstone in the management of patients with inherited coagulation defects.

Keywords: Protein S deficiency, blighted ovum, thromboprophylaxis, anticoagulation, thrombophilia

Acquired or hereditary thrombophilia occurs in almost two-thirds of women presenting with recurrent miscarriages, pre-eclampsia, intrauterine growth retardation, abruptio placentae or stillbirth, which are associated with microvascular thrombosis in placental blood vessels. Protein S deficiency is associated with a variably increased risk of thrombosis and is inherited independently in an autosomal dominant trait. Here we report such a case with protein S deficiency with a successful maternal and fetal outcome.

CASE REPORT

A 27-year-old woman, Gravida 3, with history of two blighted ovum in the past, presented in April 2016 for preconceptional counseling. Her first pregnancy in 2015 was spontaneous conception that ended in blighted ovum (8-9 weeks). She underwent curettage. Her second pregnancy in January 2016 was again spontaneous conception that again ended in blighted ovum (9-10 weeks), where yolk sac was seen but fetal pole was not developed. In both instances, patient had no other intra- or postoperative complications and was discharged on contraceptive advice. Investigations carried out on her during interval period revealed cytomegalovirus (CMV), herpes simplex virus (HSV) and Rubella IgG positivity in nonsignificant titers, and deficient protein S activity of 32%. Other thrombophilia screening, protein C, antithrombin III, factor V leiden levels were normal. Lupus anticoagulant (LA), anticardiolipin antibody (ACLA), antinuclear antibody (ANA), anti-double stranded DNA antibody (anti-ds-DNA), sugars, Venereal Disease Research Laboratory (VDRL) were negative, including normal parental karyotyping. The couple was advised to take hematological opinion and was counseled about autosomal dominant nature of protein S deficiency. The patient was advised periconceptional folic acid and early antenatal care (ANC) registration and thromboprophylaxis in next pregnancy.

She conceived in September 2016 and registered at the antenatal clinic where I was consulting. Her baseline complete blood count and coagulation profile were within normal limits. In view of protein S deficiency, the patient was started with low molecular weight heparin (LMWH) 60 units subcutaneous once-daily from same day when her urine pregnancy test (UPT) was found positive and aspirin 75 mg once a day after dinner, once cardiac activity was confirmed in her first scan around 6-7 weeks. The patient was monitored for symptoms of bleeding during pregnancy. Her nuchal translucency (NT) scan, combined test, anomaly scan all were normal. She was given two doses of betamethasone intramuscular around 28 weeks. Color Doppler at 32 weeks showed good interval growth with normal Doppler flows. She underwent weekly nonstress test (NST) and biophysical profile from 32 weeks onwards for antepartam fetal surveillance.

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Aspirin was stopped around 34 weeks. Doppler was again repeated around 36-37 weeks, and was normal. Elective lower segment cesarean section (LSCS) was planned at 38 weeks, and LMWH was stopped 12 hours before surgery. She delivered a male child of 3 kg with good Apgar score on 10th May 2017.

Neonate was evaluated by pediatrician and was found to be normal. Injection LMWH was restarted on the day after surgery. Warfarin 1 mg o.d. was also started. Warfarin doses were stepped up and adjusted up to 5 mg o.d. with daily monitoring of prothrombin time/international normalized ratio (PT/INR) values. Heparin was discontinued once INR levels were in the range of 2-3. The patient was advised to continue warfarin for 6 weeks after discharge.

DISCUSSION

Protein S deficiency is associated with a variably increased risk of thrombosis and is inherited independently in an autosomal dominant trait. The protein S gene is located on chromosome 3. Over 90 different mutations in protein S gene have been found.

Incidence of symptomatic protein S deficiency is 1:20000. Anticoagulant therapy is the cornerstone in the management of these patients.

The cerebrovascular system may be primarily involved in young adults suffering from anticoagulants deficiency. Considering the importance of prothrombotic state, especially caused by deficiency of protein S, any patient presenting with features of cerebrovascular accidents should be thoroughly investigated for any natural anticoagulant deficiency, in whom no other etiological factors can be determined. Hence, thrombophilia screening might be justified in women with pregnancy loss and treatment with LMWH might be considered for those with pregnancy loss and thrombophilia. Women with thrombophilia are also prone to venous thromboembolism in pregnancy and puerperium.

Many women with a history of recurrent miscarriage are at greater risk of pre-eclampsia, intrauterine growth retardation and intrauterine fetal death, which suggests that these adverse pregnancy outcomes represent a spectrum of disorders which share a common origin. Special care and precautions should be taken in postoperative period to prevent the catastrophic event of venous thromboembolism, which could lead not only to major morbidity, but also mortality.

CONCLUSION

Patients with protein S deficiency may remain asymptomatic or present with thromboembolic incidents and bad obstetric history. Anticoagulant prophylaxis should be considered weighing the risk of bleeding to thromboembolic recurrence.

SUGGESTED READING

1. Hayashida M, Yamada H, Yamazaki S, Nomura H, Yoshimura K, Kitahara O, et al. Combined protein C and protein S deficiency in a family with repetitive thromboembolism and segregated gene mutations. Intern Med. 2003;42(3):268-72.
2. Formstone CJ, Hallam PJ, Tuddenham EG, Voke J, Layton M, Nicolaides K, et al. Severe perinatal thrombosis in double and triple heterozygous offspring of a family segregating two independent protein S mutations and a protein C mutation. Blood. 1996;87(9):3731-7.
3. Plutzky J, Hoskins JA, Long GL, Crabtree GR. Evolution and organization of the human protein C gene. Proc Natl Acad Sci U S A. 1986;83(3):546-50.
4. Schmidel DK, Tatro AV, Phelps LG, Tomczak JA, Long GL. Organization of the human protein S genes. Biochemistry. 1990;29(34):7845-52.
5. Reitsma PH, Bernardi F, Doig RG, Gandrille S, Greengard JS, Ireland H, et al. Protein C deficiency: a database of mutations, 1995 update. On behalf of the Subcommittee on Plasma Coagulation Inhibitors of the Scientific and Standardization Committee of the ISTH. Thromb Haemost. 1995;73(5):876-89.
6. Gandrille S, Borgel D, Ireland H, Lane DA, Simmonds R, Reitsma PH, et al. Protein S deficiency: a database of mutations. For the Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Thromb Haemost. 1997;77(6):1201-14.
7. Protein C deficiency. eMedicine. Available at http://emedicine.medscape.com/article/205470.
8. Martinez HR, Rangel-Guerra RA, Marfil LJ. Ischemic stroke due to deficiency of coagulation inhibitors. Report of 10 young adults. Stroke. 1993;24(1):19-25.
9. Barinagarrementeria F, Cantú-Brito C, De La Peña A, Izaguirre R. Prothrombotic states in young people with idiopathic stroke. A prospective study. Stroke. 1994;25(2):287-90.
10. Pabinger I. Thrombophilia and its impact on pregnancy. Thromb Res. 2009;123 Suppl 3:S16-21.
11. Vormittag R, Pabinger I. Thrombophilia and pregnancy complications. Hamostaseologie. 2006;26(1):59-62.
12. Regan L, Rai R. Thrombophilia and pregnancy loss. J Reprod Immunol. 2002;55(1-2):163-80.

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