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Case Report

HEREDITARY PROTEIN S DEFICIENCY AND RECURRENT VENOUS THROMBOSIS: A CASE REPORT

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SUMMARY – A case is presented of a 32-year-old female with hereditary protein S deficiency associated with pulmonary embolism and recurrent deep venous thrombosis of lower extremities. Other proteins known to be associated with familial thromboembolic disease, including antithrombin, plasminogen, fibrinogen, protein C, factor V Leiden and prothrombin G20210A, were normal. Her mother, grandmother and great-grandfather had a history of thromboembolic disease. This report illustrates the importance of protein S measurement in patients suspected of having inherited venous thrombotic disorders.

Key words: *Blood proteins; Glycoproteins – deficiency; Protein S – deficiency; Thrombophilia – etiology; Venous thrombosis – genetics*

Introduction

Protein S is a vitamin K dependent plasma glycoprotein (MW 70,000) that acts as a cofactor for activated protein C (APC) in preventing coagulation and stimulating fibrinolysis. It stimulates inactivation of factor Va and cofactor VIIIa by APC in both plasma and purified systems. Protein S forms a 1:1 complex with APC on phospholipid surfaces and is therefore thought to stimulate the phospholipid-dependent inactivation of factors Va and VIIIa. Thrombophilia caused by protein S deficiency was first reported in 1984 and has subsequently been established as a risk factor for venous thrombosis[1]. Protein S is synthesized in the liver, endothelial cells, brain cells, kidney, testicular cells and megakaryocytes[2-4]. The biologic half-life of protein S is 30-60 h[5]. In plasma, only 40% of protein S are available in the free form, whereas the remainder is bound to C4b-binding protein and cannot interact with APC[6]. Only free protein S has a cofactor activity for APC. Physiologic variations include a lower mean free protein S level in normal females than in normal males, and lower total and free protein S in newborns. Protein S deficiency may be an inherited or acquired disorder, which is a risk factor for venous thrombosis. Protein S deficiency shows the autosomal dominant pattern of inheritance. Three types of hereditary deficiencies have been identified. In type I deficiency, there is a 50% or greater reduction in total protein S antigen. Type II is a qualitative deficiency (normal total and free protein S antigen levels but abnormal functional activity). In type III deficiency free protein S antigen is reduced, while total protein S is within the normal range. There are multiple causes of acquired protein S deficiency. Reduced levels of total protein S have been reported during pregnancy and with the use of oral contraceptives and anticoagulants, in patients with acute thrombosis and those with liver disease. Protein S levels are commonly low in inflammatory states and are largely due to increased C4b-binding protein (acute phase reactant) complexing with protein S. The levels of total and free protein S are significantly reduced in men with human immunodeficiency virus infection.

Case Report

The propositus was a 32-year-old female with a history of thromboembolic disease that had begun at the age of 24, in 1996. She developed right calf vein thrombosis and

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was treated with oral anticoagulants for six months. In 2003, four weeks after delivery, she developed ileofemoral thrombosis in her left leg again, complicated by pulmonary emboli. Clinical diagnosis was confirmed by doppler sonography and pulmonary perfusion scintigraphy. The patient was treated with intravenous unfractionated heparin and subsequently with oral anticoagulants. Her family history revealed numerous episodes of thrombosis. Her mother, now aged 64, developed right calf vein thrombosis after delivery when she was 32 years old, and left calf vein thrombosis 21 years later. The patient's grandmother died from pulmonary emboli when she was 50 years old, after operative treatment. The patient's great-grandfather suffered from thrombophlebitis and deep venous thrombosis. Laboratory studies of plasma obtained from the propositus and her mother showed normal values of prothrombin time, partial thromboplastin time, antithrombin, plasminogen, fibrinogen, protein C and thrombin time, but a low concentration of total protein S (10% of normal values in the propositus and 30.5% in her mother). No evidence of liver disease or disseminated intravascular coagulation was observed at the time of plasma collection. Anticardiolipin and antinuclear antibodies were negative. Based on these findings, we concluded that total protein S deficiency (type I) was the cause of the familial thromboembolic disease.

Discussion

Protein S is a vitamin K-dependent protein that enhances the anticoagulant effect of activated protein C. The lack of protein S causes a disturbance of anticoagulation. Protein S deficiency is an autosomal dominant disorder. The prevalence of protein S deficiency in thrombotic patients has been estimated to 1 *per* 33,000[7]. Protein S decreases significantly during pregnancy due to increasing plasma volume and dilution[8]. Patients with protein S deficiency are at an increased risk of thromboembolic disease. The incidence of spontaneous thrombosis in patients with protein S deficiency is estimated to 0.4% *per* year[9]. During the periods of high clinical risk such as pregnancy, delivery, and post partum period, the incidence of thromboembolic disease rises to 4.1% *per* pregnancy[9]. Thus, all patients with personal or family history of thromboembolic disease should be considered for antenatal prophylaxis and screening for thrombophilia. It is preferable to investigate patients suspected of having protein S (or protein C) deficiency after oral anticoagulants have been discontinued for at least one week. May it be impossible to discontinue warfarin because of the severity of thrombotic diathesis, such individuals can be studied while receiving heparin therapy, which does not alter plasma protein S concentrations. Women with thrombophilia including protein S deficiency and a history of previous thromboembolic disease should receive thromboprophylaxis during pregnancy and 6- to 8-week post partum period. Low-molecular-weight heparin appears to be a safe alternative to unfractionated heparin or oral anticoagulants for both the fetus and the mother[10]. Our patient did not receive any prophylaxis after delivery, so the risk of thrombosis was much greater.

Sometimes it is difficult to diagnose familial protein S deficiency. Repeat sampling and family studies are usually required to make definitive diagnosis. We do not know the exact incidence of hereditary protein S deficiency in the Croatian population. So, additional studies are needed to define the prevalence of protein S deficiency in Croatia.

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Sažetak

NASLJEDNI NEDOSTATAK PROTEINA S I OPETOVANE TROMBOEMBOLIJE

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Prikazan je slučaj 32-godišnje bolesnice s nasljednim nedostatkom proteina S povezanim s plućnom embolijom i opetovanom dubokom venskom trombozom donjih ekstremiteta. Ostali čimbenici nasljedne trombofilije, tj. antitrombin, plazminogen, fibrinogen, protein C, faktor V. Leiden i protrombin G20210A su bili uredni. Obiteljska anamneza majke, bake i pradjeda ukazivala je na opetovanu vensku trombozu i plućnu emboliju. Navodi se značenje određivanja proteina S u bolesnika sa sumnjom na nasljednu trombofiliju.

Ključne riječi: *Krvni proteini – deficijencija; Protein S – deficijencija; Trombofilija – etiologija; Venska tromboza – genetika*