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A rare case of Deep Vein Thrombosis due to combined deficiency of Protein C and Protein S

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Abstract

Protein C and protein S act as anticoagulants by degrading the activated factors V and VIII. Deficiency of these factors, acquired or hereditary, are associated with increased risk of venous thrombosis. A patient having combined deficiency of both factors protein C and protein S is very rare.

Here, we report a 60 year-old Indian female who presented with pain and swelling of the right lower extremities. Venous Doppler showed deep venous thrombus in the right common femoral vein and distal deep veins and further evaluation of coagulation profile showed combined deficiency of both protein C and S. She was started on long-term anticoagulant therapy and she is doing well with the treatment provided.

Deep vein thrombosis due to combined deficiency of protein C and protein S is extremely rare. Anticoagulation therapy is the cornerstone in the management of patients with inherited coagulation defects.

Keywords: Protein C, Protein S, Combined deficiency, Thrombophilia, Deep Vein Thrombosis

Introduction

Venous thromboemboli arises in conditions of stasis, hypercoagulability, and acute trauma to venous endothelial surfaces. Hypercoagulable states may be acquired (antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, malignancy, pregnancy, nephrotic syndrome, or estrogen therapy) or inherited (prothrombin gene mutation, protein C and S deficiency, antithrombin III deficiency, factor V Leiden, or hyperhomocystinemia).

Protein C is a vitamin K dependent anticoagulant. Protein S acts as a cofactor for activated protein C.[1] These activated protein C/protein S complex proteolyses procoagulant factors V and VIII, thereby retarding fibrin formation and by preventing activation of procoagulant proteins, factor X and prothrombin. [2] Hereditary deficiency of both protein C and protein S are associated with increased risk of venous thrombosis[3] or rarely, arterial thrombosis.[4,5] Both of these deficiencies are inherited independently in an autosomal dominant trait. Each of these deficiencies is seen in 5% to 10% of the patients with deep vein thrombosis or pulmonary embolism.[6,7] Combined deficiency of protein C and protein S is rare and only few confirmed cases with genetic decoding has been reported.[7,8]

Here, we report a similar case of combined deficiency of both proteins C and S presenting as deep vein thrombosis.

Case Summary

A 60-year-old Bengali female with known hypertension presented in the emergency department with complaints of pain and progressive swelling of the right lower limb for 3

days. She had undergone a cholecystectomy 6 years back for symptomatic cholelithiasis. Her medications included only Losartan. No other members in her maternal and fraternal families had a similar illness. There is no history of consanguineous marriage in the family. Physical examination was insignificant except for swelling and pitting edema on her right lower limb.

On investigation, she was mildly anemic with haemoglobin of 9.5 gm/dl, erythrocyte sedimentation rate (ESR) of 54 mm in first hour. Her complete blood count with differential, bleeding time, clotting time, prothrombin time/international normalized ratio (PT/INR), serum electrolytes, and liver function tests were all within normal limits. Chest x-ray and ultrasound abdomen/pelvis showed normal findings. Contrast enhanced computed tomography of the chest was negative for pulmonary embolism.

Venous Doppler showed subacute deep vein thrombosis of right common femoral vein and distal deep veins.

She was started on subcutaneous low molecular weight heparin (LMWH). Investigations on the thrombophilia profile was sent and it revealed protein C 56.9 units/ml (Normal 70-140 units/ml), protein S 14units/ml (Normal-55-123 units/ml), anti thrombin III 110 units/ml (Normal-80-120units/ml). PCR of factor V Leiden mutant, factor V Cambridge mutant, factor II mutant, and methyelenetetrahydrofolate reductase mutant were negative.

A repeat functional assay of protein C and protein S was done 2 weeks later to confirm if the previous values were false positive. They also revealed protein C 53.4 units/ml (Normal 70-140 units/ml) and protein S 18 units/ml (Normal 55-123 units/ml).

Patient was thereafter overlapped with oral Warfarin therapy with discontinuation of LMWH when PT/INR was in a range of 2-3 on serial follow-up. Since then, the patient has been doing well on Warfarin with regular close monitoring of INR.

Discussion

Protein C and Protein S deficiencies are associated with a variably increased risk of thrombosis and are inherited independently as an autosomal dominant trait. The protein C gene resides on chromosome 2 [9] while the protein S gene is

located on chromosome 3.[10] It has been found that over 160 different mutations on the protein C gene[11] can lead to absence, or a defective form, of protein C and there are over 90 different mutations of protein S gene.[12] Incidence of clinically symptomatic protein C deficiency lie between 1:16 000 to 1:32 000 persons while that of symptomatic protein S deficiency is 1:20 000.[8,13] Incidence of severe protein C deficiency presenting as inherited homozygous or compound heterozygous state is very rare, occurring in 1:500 000 to 1:750000.[13] Combined protein C and protein S deficiencies are still rare and very few cases have been reported in the literature.

Koller et al documented protein C and S deficiency in association with strokes in young women.[14] Similar cases of combined deficiency of protein C and S have been described by Atkins and Zehnder [15] on a 46-year-old female with mesenteric artery thrombosis and Onwuanyi et al [16] on a 48-year-old female with multiple aortic thrombi.

Patients with protein C or protein S deficiency have an increased risk of thrombosis with age, especially after 20 years of age. [17,18] Combined protein C and S deficiency not only increases the episodes of thromboembolism but also manifest early vascular incidents. [7,17,18] However, in our case the presentation was not at an early age. Also, none of the patient's family members had any episodes of vascular incidents, which is quite unusual. In families

with combined protein C and S deficiency, only a few carriers have been reported without the history of thrombosis and the incidence of the thrombotic events among patients or carriers is not known. [7,17,18]

Diagnosing the patients with protein C or S deficiency is by showing low levels of these factors usually by immunological or functional assays. In a patient with heterozygous deficiency of protein C and protein S, diagnosis may at times be difficult because of possible overlap at the lower end of the normal reference range between heterozygous and normal individuals.[19,20] Repeat testing of the patients with borderline values is therefore recommended, and family studies and genetic testing is of particular importance in such cases and in patients on oral anticoagulants. Caution should be taken while measuring these factors in an acute thrombotic state, which is usually low. In our case, repeat testing of protein S and protein C was still low but genetic testing was not feasible. While estimating the values of protein C and S on patients with oral anticoagulant, the other vitamin K dependent procoagulants of similar half-life (factor II and VII) should also be estimated to compare as oral anticoagulant decreases both protein C and S giving false low estimates. [21]

Anticoagulant therapy is the cornerstone in the management of these patients. [22] The extent of disease and the likelihood of recurrence must be carefully assessed before placing a patient on long-term anticoagulant therapy. However, in patients with a deficiency of more than one factor, recurrent thrombosis or strong family history of thrombosis long-term anticoagulant therapy is generally needed. [13, 23] Certain heterozygous patients with no previous history of thrombosis or no family history of thrombosis may benefit from short-term anticoagulation in high thrombotic risk states as pregnancy, postpartum, postoperative, and trauma.

Conclusion

Patients with isolated protein C or S deficiency may remain asymptomatic or present with thromboembolic incidents. But with combined deficiency of both protein C and S the risk of thrombosis is high and occurs earlier in life. Long term anticoagulant prophylaxis should be considered weighing the risk of bleeding to the risk thrombotic recurrence.

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