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A Female with Recurrent Venous Thrombosis

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Abstract:

A 50- year-old female was presented with recurrent venous thrombosis with ischemic stroke due to protein S deficiency. Other causes of recurrent venous thrombosis were excluded by different investigations. We only found low level of protein S. In most of the cases, thrombophilia screening is not usaally done. So, this report will illustrate the importance of thrombophlia screening in patient having recurrent venous thrombosis.

Keyward: *Protein S- deficiency, Thrombophilia-Aetiology, Thromboembolism*

Introduction:

The term "hypercoagulable state" is generally used to denote any conditions in which the normal balance between clotting and anti-clotting mechanisms become altered in such a way that the patient is predisposed to thrombus formation. 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 fibrin. It stimulates the activation of factor Va and cofactor VIIIa by preventing APC in both plasma and purified systems. Protein S forms a 1:1 complex with APC on phospholipids surfaces and is thought to stimulate the phospholipids 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 hour.[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 .It is also found low in 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. Aim of the reporting this case is rarity of incidence of protein S deficiency and increase the awareness for identification of the causes of venous thrombosis.

Case Report:

A 50 years old female, muslim, married, house wife, normotensive and nondiabetic came from Suritola, Dhaka on 21.06.2010 through was admitted through Emergency department with the complaints of altered consciousness and right sided weakness for 1 day and recurrent swelling of left lower limb for 4 months .According to the statement of the patient as well as her attendant , she was well about 4 months back. Then she developed sudden swelling of her left lower limb. It was an association with dull aching discomfort and itching. Symptoms are aggravated by prolong standing and towards the end of the day. There is dark black discoloration in the lower third of the left leg more marked in the medial aspect. During her illness, she developed swelling of her left lower leg recurrently and she went to the local

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physician several times. The physician prescribed some oral medications every time. After taking medication ,the swelling subsided for a few days but again recurred. Patient gave no a history of bed rest due to illness , trauma, fracture, swelling of the leg or any other parts of the body like face. It was not associated with intermittent claudication. It was followed by sudden development of altered consciousness and right sided weakness with loss of ability to speak for 1 day. It was not associated with headache, vertigo or trauma. Her pulse was 92 beats/min and blood pressure was 130/90 mm Hg. During inspection, almost whole leg up to hip was swollen. There was dark black discolouration in the lower one third, more marked in the medial aspect without any excoriation or ulceration. On palpation, temperature was slightly raised, skin was dry and pulse was present. Calf tenderness and pitting oedema were also present. Regional lymph nodes were not palpable. Homan's sign was not done. Burger test was negative. On neurological examination, right planter reflex is extensor, right sided other jerks in lower limb slightly exaggerated. GCS 15/15.Sensation was normal. Other systemic examination revealed no abnormality. This patient was diagnosed as a case of Deep vein thrombosis and stroke (ischemic) with right sided hemiparesis. Clinical diagnosis was confirmed by Doppler study of lower limbs and CT scan of the brain.

Laboratory studies of this patient showed normal value of prothombin time , activated partial thrombin time, protein C , antithrombin III.and homocystine level (8 umol/L) but lower concentration of protein S (47% Normal: 60-130%). Antinuclear factor (ANA),Anti ds DNA and Antiphospholipid antibody are negative No evidence of liver disease and disseminated intravascular coagulation was observed at the time of plasma collection. Based on these findings we concluded that total protein S deficiency was the causes of deep vein thrombosis.

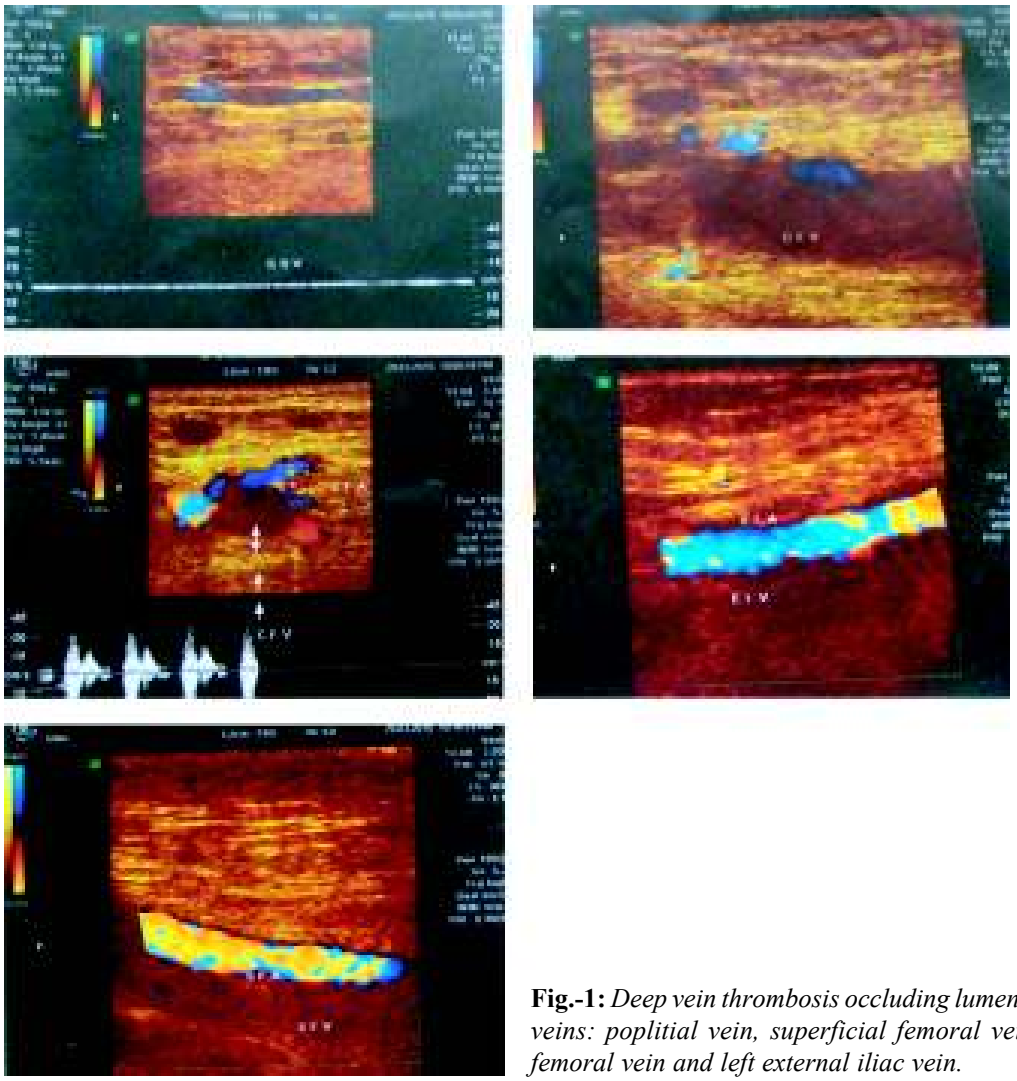

Fig.-1: *Deep vein thrombosis occluding lumen of all left leg veins: poplitial vein, superficial femoral veins, common femoral vein and left external iliac vein.*

Table-I

Thrombophilia Screening

Investigation	Result	Reference range
Fibrinogen	298 mg/dl	180-350 mg/dl
D- Dimer	0.62 mg/l FEU	<0.55 mg/l FEU
Protein C	76%	70 -140%
Protein S	47%	60-130%
Anti thrombin	78%	75 -125%
Homocystine	8µmol/L	6-12µ mol/L

Discussion:

Protein S is a vitamin k dependent protein that enchances the anticoagulant effect of activated protein C. The prevalence of protein S deficiency in thrombotic patient has been estimated to 1 per 33,0000. The incidence of spontaneous thrombosis in patient with protein S deficiency is estimated to 0.4% per year. The exact incidence of protein S deficiency in our population is not known. Clinically, patients with protein S deficiency is at increased risk for venous thromboembolic disease, ocasional arterial thrombosis, and even portal vein thrombosis.[7-9] Our patient had both venous thrombosis (DVT) and arterial thrombosos (Ischaemic stroke) with low protein S level. Acquired causes of protein S deficiencies are seen in acquired illness like liver disease, DIC, therapy with L-asparaginase and coumarin, and acute severe bacterial infections etc[10-11] which were not present in our patient at the time of presentation and before presentation. The management of these patients with deep vein thrombosis was done with low molecular weight heparin along with warfarin and was advised to avoid dehydration at any cost as a preventive measure[5]. All patient with recurrent thromboembolic disease should be screened for thrombophilia. Sometimes it is difficult to diagnose whether protein S deficiency is hereditary or acquired. Repeated sampling and family studies are usually required to make definite diagnosis. We do not know the exact incidence of protein S deficiency in our population. . So, additional studies are needed to define the prevalence of protein S deficiency in our population.

Conflict of Interest: None

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