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Original Research Paper

General Medicine

PROTEIN C DEFICIENCY CAUSING RECURRENT DEEP VEIN THROMBOSIS (DVT) IN A YOUNG MALE: CASE REPORT.

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ABSTRACT Protein C deficiency (PCD) is a rare genetic disorder that occurs due to mutation in PROC gene and results in increased predisposition to thrombosis, PCD can be 'autosomal dominant 'which is relatively more common occurs in adults and usually presents as recurrent DVT, ischemic colitis or may remain asymptomatic. 'Autosomal recessive PCD' is relatively rare, more severe and presents in neonates as 'neonatal purpura fulminans'. I report a case of 41-year-old male who came with history DVT (recurrent) and diagnosed as 'Protein C deficiency: Type 1'.

KEYWORDS : Protein C, deficiency, thrombosis, DVT

CASE

41 / Male, came to Emergency room with complaints of giddiness since one day, breathlessness on exertion (NYHA Grade 3) since 3 days, Swelling over Bilateral lower limbs since one month, known case of T2 DM, HTN since 3 yrs on treatment, previous history of DVT in left lower limb 3 years back treated with warfarin for one year. Clinical examination and investigations were suggestive of heart failure and started treatment for the same.

On Day 4 of admission, patient developed Right upper limb DVT. Considering recurrent episodes of DVT, thrombophilia work up done. Patient came to be Protein C deficient (38.7) on investigations.

Diagnosis of Type 1 PCD was made and patient started on anticoagulant.

BACKGROUND/ INTRODUCTION

1) Protein C deficiency is a rare disorder that occurs due to mutation in PROC gene and results in increased predisposition to thrombosis
2) Protein C inactivates factor 5 and 7, hence preventing thrombin generation and thrombosis formation
3) Protein C deficiency can be 'Autosomal dominant' which is caused by 'Mono-allelic' mutation in PROC gene OR 'Autosomal recessive' which is caused by 'Bi-allelic mutation' in PROC gene
4) Autosomal dominant PCD is relatively more common, incidence is 1 in 200-500 people, relatively less severe, occurs in adults, affected individual can be asymptomatic or may present as single / multiple episodes of DVT [1]
5) Autosomal recessive PCD is relatively rare, affects 1 in 40000-250000 people, more severe presents in Neonatal period as Neonatal purpura fulminans [2]
6) Diagnosis is based on clinical presentation (eg: recurrent DVT episodes)
7) Protein C levels and genetic testing (if available)
8) Affected individual requires long term anticoagulation and follow up
9) Diagnosis and management of Protein C deficiency is important because if left undiagnosed, complications like limb ischemia, stroke, Heart failure, AKI, etc may occur.

CASE PRESENTATION

41 year male, Computer Engineer by occupation came to Emergency room with complaints of giddiness (2 episodes in 1 day), Breathlessness on exertion (NYHS Grade 3) since 3 days, swelling over Bilateral lower limb since 1 month. Pt was k/c/o DM, HTN since 3 yrs and was on medication for the same and was controlled. Pt had past history of DVT in Left Lower Limb (Involving lower 2/3rd of left superficial vein, entire left popliteal vein left anterior and posterior tibial veins and common peroneal veins), 3yrs back (in 2019) and had taken warfarin for 1 year and then stopped after recovery.

On General Examination, patient was conscious, oriented, vitally stable, JVP raised (11cm of water), pedal edema present, pallor/ icterus /clubbing/cyanosis absent.

On systemic Examination, Respiratory system –bilateral coarse crepitations heard in lower lobes of the lungs, Cardiovascular system – first and second heart sounds heard, no murmur; Central Nervous System is showing no abnormality; Per Abdomen – soft, non-tender, no organomegaly, no signs of ascites .

In blood investigations, Pro BNP was raised (15000 pg/ml), CPKMB, TROPONIN T were borderline high (34 u/l and 30 ng/ml respectively), LFT moderately deranged (SGOT: 200 IU/L, SGPT: 250 IU/L, Total bilirubin: 2.0, Direct bilirubin: 0.8)

PT /INR, CBC, RFT were within normal limits. USG (Abdomen +Pelvis) showed mild hepatomegaly, no ascites, 2D Echo was suggestive of Grade 3 Diastolic Dysfunction with severe left ventricular dysfunction with LVEF of 30%, Valves were normal. Patient started on standard treatment for Heart Failure. Over the time LFT improved.

On Day 4 of admission, patient developed swelling and tenderness at the site of intravenous access at the edge of right cubital fossa.

Color Doppler of Right Upper limb was done, which showed DVT (Near complete Lumen occlusion), extending from right basilic vein at the level of elbow joint and involving right axillary vein.

Considering recurrent episodes of DVT in young patient, work up was done to rule out thrombophilia and autoimmune causes. On investigations Protein C came to be deficient {38.7 (normal range: 60-166)} Whereas Protein S, Anti Thrombin 3 Levels, PT INR, aPTT, were within normal limits; ANA, Lupus Anticoagulant, Anti Phospholipid Antibody came negative .

Diagnosis of 'Type - 1 Protein C Deficiency was made based on clinical findings (recurrent episodes of DVT involving different sites) and reduced Protein C levels and patient was started on anticoagulation (low molecular weight heparin 0.6 mg s/c OD for 5 days)

Rest 3 limb's arterial and venous color Doppler was done

which showed no abnormality. Coronary Angiography was done which suggested Normal Coronaries.

Patient was discharged on oral anticoagulation (on Rivaroxaban), need of long-term anticoagulation and DVT prophylaxis was explained and was asked to follow up regularly.

Fig: Left Lower Limb Venous Doppler showing 'left poplitial vein thrombus'.

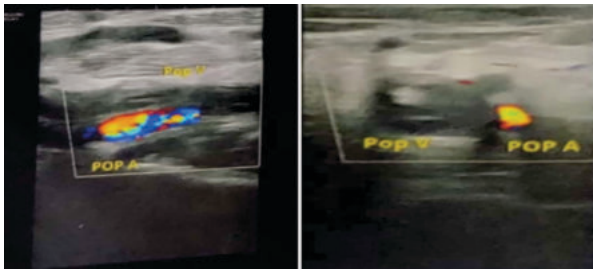
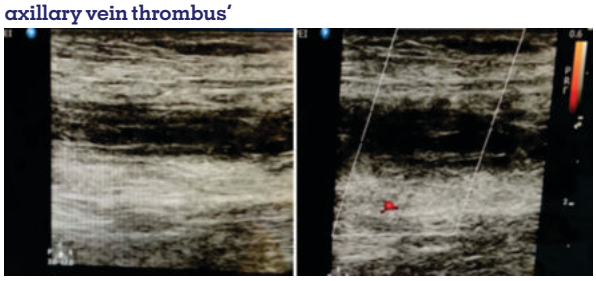


Fig: Right upper limb Venous Doppler showing 'right axillary vein thrombus'



DISCUSSION

1) Protein C is a Vitamin K dependent, important glycoprotein which is synthesized by the liver. [1]
2) Protein C is present in inactive form in blood as zymogen. [1]
3) Activation of Protein C is catalized on 'endothelial surface 'when thrombin binds to thrombomodulin. [2]
4) Activated Protein C exerts inhibitory effect on coagulation by inactivating factors 5 and 7, hence preventing thrombin generation and thrombosis formation. [3]
5) Inhibitory effect of Protein C is enhanced by Protein S. [4]
6) Protein C is encoded by PROC gene located on chromosome 2q14.3 and contains 9 exons [4]
7) Mutation in PROC gene results into decreased levels of Protein C and results in hypercoagulable state of blood and thrombosis. [7]
8) Protein C deficiency (PCD) is classified into 2 types: [8]

a. Type 1: Decreased Protein C concentration in the blood due to its defective synthesis /secretion.
b. Type 2: Decreased Activity of Protein C with normal concentration due to impaired binding of receptor/ calcium/substrate.

9) Type 1 PCD is more common Points 3), 4), 5) in Background/Introduction (regarding autosomal dominant and recessive PCD) [6]
10) PCD' can have different types of presentations [10]
11) Eg: Recurrent episodes of DVT which is commonest type of presentation [6], Ischemic colitis which is the commonest GIT manifestation of PCD [7], Heart Failure, Pulmonary embolism [8], ischemic stroke [9], Myocardial Infarction [10] [6]
12) PCD can present as recurrent miscarriage in Females [11][8]
13) Case of 19-year Female with PCD with Cerebral Venous Thrombosis with left sided subdural hematoma has been reported [12][9]
14) Pediatric patient with PCD with ocular manifestation is also reported.[10]
15) Differential Diagnosis of Protein C deficiency includes Protein S deficiency, Anti Thrombin 3 Deficiency, Disseminated intravascular coagulation, hypercoagulable state secondary to autoimmune disorders. [11]
16) Diagnosis of Protein C deficiency is based on clinical profile and history of the patient (ie recurrent thrombotic events /DVT), low Protein C levels and genetic testing (PROC Gene) if available.
17) According to clinical profile of our patient (2 episodes of DVT at different sites, low LVEF in young age secondary to diastolic dysfunction) and low Protein C levels, our patient falls in 'Autosomal Dominant Type 1 Protein C Deficiency '
18) However due to some unavoidable reason genetic testing of the patient could not happen.
19) Early diagnosis of PCD is very important to prevent recurrent DVT episodes, limb ischemia and necrosis, stroke, myocardial infarction, injury to vital organs secondary to thrombus formation.
20) Management of PCD includes 'DVT Prophylaxis ', eg: DVT stockings in high-risk case and prolong anticoagulation with oral anticoagulants (eg: Direct Factor Xa inhibitors – Rivaroxaban, Apixaban, Direct Thrombin inhibitors –Dabigatran, Vitamin K antagonists – Warfarin). [14]
21) In patients with PCD, warfarin should be used with caution as they are at increased risk of developing 'Warfarin Induced Skin Necrosis. [15]

CONCLUSION

Early diagnosis of PCD based on clinical profile of patient, past history of thrombotic events and protein C levels and appropriate treatment with anticoagulants is important to prevent complications of PCD like limb ischemia/ necrosis /stroke/ MI/ Heart failure / Ischemic colitis etc.

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