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CASE REPORT

Sagittal sinus thrombosis in a patient with familial Protein C deficiency: Highlighting the impact of thrombophilia testing

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Abstract

Plasma protein-C is a natural anticoagulant that inactivates factors Va and VIIIa. Familial protein C deficiency is inherited as an autosomal dominant disorder. The homozygous or compound heterozygous type may present early as purpura fulminant, while the heterozygous type can present as thromboembolism later in life. Presented in this report is a case of a 21-year-old female patient with protein-C deficiency, confirmed by thrombophilia investigations. She experienced recurrent deep vein thrombosis and cerebral sinus thrombosis due to thrombotic occlusion. She had a family history of deep vein thrombosis. Hence, high-risk cases should be seriously considered for long term anticoagulation therapy. The utility versus futility of thrombophilia testing in a particular situation is discussed to address and ensure safe practice among patients with thromboembolism.

Keywords: thrombophilia, protein C, thrombosis, hereditary

INTRODUCTION

Thromboembolism (TE) is either hereditary, acquired or a combination of both. The heterozygous form can be found at a rate ranging from 1 in 200 to 1 in 500 in the various healthy human populations.[1] Its events commonly occur following a wide range of triggers including infection, pregnancy, cancer, trauma, and surgery. In addition, certain medications such as some contraceptive pills and hormone replacement therapy must be excluded before considering the hereditary type.[2] The common hereditary factors are protein C, protein S, and antithrombin deficiency. Inherited protein C (PC) deficiency is an autosomal dominant disorder associated with venous thrombosis. Individual with PC deficiency has 10 to 15 folds risk to develop venous embolism.[3] It occurs mainly in the veins of the lower extremity, but may also occur in the brain, renal system, or gastrointestinal system.[4,5] In this case report, a patient with PC deficiency presented with neurological manifestations due to cerebral sinus thrombosis. The case highlights the potential of PC deficiency to have multiple thrombotic presentations and be presented during early adult life. The dilemma in thrombophilia testing is also discussed.

CASE REPORT

A 21-year-old female patient presented at the Emergency Unit, Universiti Sains Malaysia Teaching Hospital, with right lower limb weakness that started one day prior to admission. Four days before admission, she had a sudden onset of headache, nausea and vomiting. Two days later, she developed a sudden right calf pain involving the right knee and ankle. She also developed behavioural changes where she became more talkative but was not associated with hallucinations, delusions, or abnormal movements. One day before admission, she had a sudden onset of weakness and numbness of the right lower limb after taking a bath. She started dragging her right foot during walking but was able to stand up from a sitting position. On the day of admission, she developed generalised tonic-clonic seizure associated with the up-rolling eyeball and drooling of saliva. It lasted

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for one minute and aborted spontaneously. She was urgently referred to a tertiary hospital for further evaluation. She denied symptoms of palpitation, shortness of breath, joint pain, oral ulcer, or hair loss recently.

Her medical history verified that she had been admitted to hospital twice due to deep vein thrombosis, confirmed by Doppler ultrasound. Her autoimmune disease screenings were negative. She was given subcutaneous fondaparinux and upon discharge, she was changed to oral anticoagulant (warfarin). However, she defaulted follow-up. She denied taking oral contraceptive pills (OCP) or traditional medicines. Two of her sisters were diagnosed with deep vein thrombosis (DVT) at the ages of 17 years and 14 years.

The clinical examination revealed that she was conscious with normal blood pressure. Her attention span and calculation were significantly impaired. She had finger agnosia and left-right disorientation, which point towards a parietal lobe syndrome. Motor system examination revealed reduced muscle power and brisk reflex of both lower limbs with an upgoing plantar response. Her respiratory and cardiovascular examinations were unremarkable.

The laboratory investigations revealed leukocytosis with a white cell count of $20x10^9$/L. The haemoglobin and platelet counts were within the reference ranges. The coagulation screening, renal and liver functions' profiles were also normal. The D-dimer was elevated (>20ug/ml). Autoimmune disease screening, lupus anticoagulant test, and infective disease screening were all negative. Computed tomography (CT) venography and magnetic resonance venography (MRV) of the brain showed large bifrontal intraparenchymal haemorrhage with a long segment filling defect within the superior sagittal sinus (Figures 1 and 2). Adjacent cortical veins were also engorged. Thrombophilia study showed a markedly low PC (Table 1). The patient was diagnosed as having PC deficiency causing cerebral sinus thrombosis. She was started on subcutaneous fondaparinux and was changed to oral anticoagulant (warfarin) upon discharge. As this was the third event of VTE, she was planned for lifelong anticoagulant, and counselling on the hereditary risk factor was undertaken. However, in this case study, the investigation of hereditary thrombophilia is not mandatory for the determination of lifelong anticoagulant therapy.

DISCUSSION

PC deficiency is a rare hereditary disorder and engenders a prothrombotic state. This is the one of the rarely reported case of PC deficiency related to sagittal sinus thrombosis in the multiethnic population. Many heterozygous individuals remain asymptomatic throughout life.[6] However, some may have thromboembolic events.[7] The severity of the deficiency is defined according to the levels of PC activity assessed by chromogenic (amidolytic) or coagulometric (clotting) assay.[8] "Mild," "moderately severe" and "severe" PC deficiencies are defined as the range of >20 IU/dL but below the age-appropriate lower limit of normal value, 1-20 IU/dl, and <1 IU/ dl, respectively.[9]

Studies have shown that family members who are PC deficient are at 7.8 folds increased risk of venous thrombosis.[10] This patient has a strong family history of thrombosis with two sisters having had DVT at young ages, and both with confirmed PC deficiency. Most patients become symptomatic after their early twenties, with increasing numbers experiencing thrombotic events by the age of 50.[11] By the age of 21, the presented patient had had three recurrent episodes of TE events. However, an accurate diagnosis for cerebral venous thrombosis (CVT) can be challenging in young patients since numerous disorders can predispose to cerebrovascular events. The typical clinical manifestations of CVT are headache (89%), focal deficits (50%), and seizures (35%).[12] Magnetic resonance imaging together with MRV is the primary

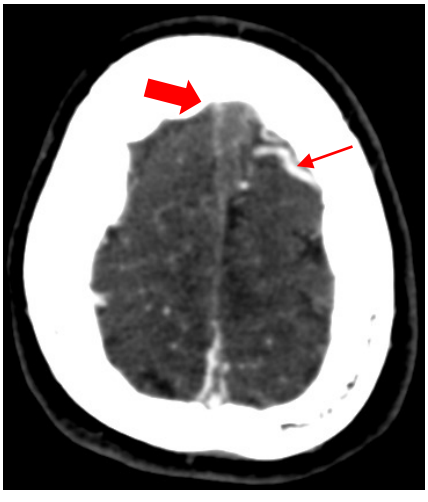

FIG. 1: CT venogram shows filling defect within superior sagittal sinus (thick arrow) with engorged adjacent cortical veins (thin arrow)

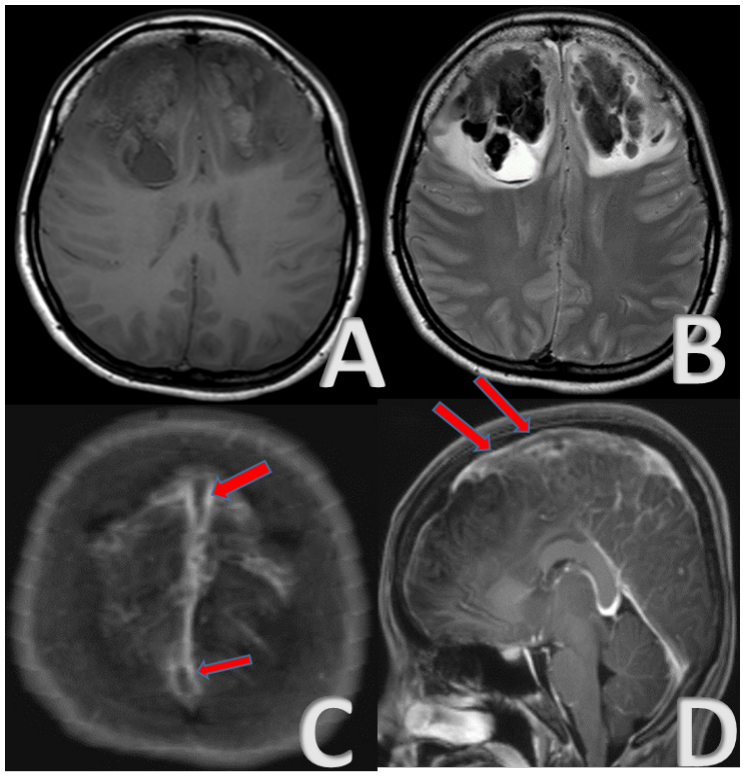

FIG. 2: MRI brain axial T1(A) and T2(B) demonstrate bifrontal intraparenchymal haemorrhage of different ages. MR venogram axial(C) and sagittal (D), shows a similar filling defect seen in CT venogram within superior sagittal sinus (arrow).

diagnostic tool in establishing this diagnosis.[12]

Thrombophilia investigation is indicated in clinical practise but not routinely performed for all patients presented with TE events. The guidelines for hereditary thrombophilia investigation have clearly outlined the indications and timing of the tests to be requested. Most guidelines and experts suggest a conservative approach to thrombophilia testing, given their limited clinical utility, and that the results of such testing may not affect patient management, especially during the acute thrombotic event.[13] Yet, when a strong family history would be evident, it would then be essential to conduct a hereditary thrombophilia study. However, precaution on result interpretation and implications to the patient management must be seriously considered, especially life-threatening events. Clinicians need to be aware of the challenges in thrombophilia testing, including preanalytical and interpretation issues. In the current case, the cause of the TE event became

Table 1: The coagulation profile of the PC deficiency patient

Test	Patient value	Reference range
Protein-C activity, plasma	6.2 IU/dl	60-150 IU/dl
Protein-S activity, plasma	106 IU/dl	60-150 IU/dl
Free Protein-S, plasma	58.6 IU/dl	Female: 57.6 - 112.5 IU/dl
Antithrombin activity, plasma	148 IU/dl	60-150 IU/dl
Factor V Leiden mutation	Not detected	
Lupus Anticoagulant		
dRVVT	33.7 sec	Cut off point 45.8 sec
dRVVT T: C Ratio	1.00	Screen ratio < 1.2

dRVVT: Diluted Russell Viper Venom Time, T; test, C: control

Table 2: Potential issues or challenges of hereditary thrombophilia testing in clinical practise

	Potential issues/ challenges in clinical practise
Preanalytical	(a) Wrong timing (eg: during the acute event) (b) On anticoagulant therapy (eg: warfarin/ heparin may lead to a reduction in PC, PS and antithrombin level) (c) Early anticoagulant therapy (not accurate)
Analytical	Test method (interference)
Post analytical	Interpretation error Implications on treatment

almost obvious; hence appropriate management was undertaken. Particularly for this patient with the strong family history, and with the patient's previously reported attempt to stop the anticoagulant therapy, testing of hereditary thrombophilia would be indicated. However, history should already suggest lifelong treatment with or without a positive test.

There are areas of dilemma and pitfalls in thrombophilia testing, including to do and not to do the test in addition to other variables that should be considered. The various issue needs to be addressed at preanalytical, analytical, and post-analytical stages of the thrombophilia testing to ensure the result reliability and patient safety (Table 2). Thrombophilia testing continues to be performed inappropriately in a high proportion of cases, especially for inappropriate clinical indications. Debates still continue about the utility versus futility of thrombophilia testing in certain situations.

CONCLUSIONS

Sagittal sinus thrombosis is a rare presentation of hereditary protein C deficiency, and it can be a life-threatening event. This clinical case demonstrates the importance of considering protein C deficiency in the diagnosis of cerebral venous thrombosis in young adults. Early recognition and accurate diagnosis of this rare hypercoagulable state may prevent recurrent thrombotic events and serious complications. Indications and implications of thrombophilia testing should be known by treating doctors.

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Conflict of interest: The authors declare no conflict of interest.

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