Case Report



Acta Haematol 2008;119:158–161 DOI: 10.1159/000126200 Received: November 27, 2007 Accepted after revision: January 28, 2008 Published online: April 24, 2008

A Case of Hereditary Protein S Deficiency Presenting with Cerebral Sinus Venous Thrombosis and Deep Vein Thrombosis at High Altitude

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Key Words

Cerebral sinus venous thrombosis · Deep vein thrombosis · High-altitude thrombosis · Protein S deficiency · Thrombosis

Abstract

A 35-year-old healthy male with no history of any past medical illness developed severe headache, vomiting and drowsiness while at high altitude (4,572 m) in the eastern Himalayan ranges. He was evacuated to a tertiary-care hospital where he was diagnosed to have cerebral sinus venous thrombosis (CSVT) on magnetic resonance imaging, with deep vein thrombosis (DVT) of his right popliteo-femoral vein on color Doppler study. Investigation for thrombophilia revealed protein S (PS) deficiency in this patient. Family screening revealed low levels of PS in two elder brothers. One brother had a history of 'stroke in young' at the age of 20 years with the other being asymptomatic. This established the hereditary nature of PS deficiency. We are not aware of any previously published report on hereditary PS deficiency combined with CSVT and DVT occurring at high altitude. However, 1 case of protein C deficiency with CSVT has been reported previously.

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Introduction

Protein S (PS) deficiency is a well-known cause for thrombophilia. It was discovered in Seattle, hence named protein S [1]. PS is a vitamin-K-dependent plasma glycoprotein (84 kDa) synthesized in the liver and endothelial cells. It is a co-factor for activated protein C (PC) and forms a complex with C4b-binding protein. PS can be free or bound; only the free form of PS is active as a naturally occurring anti-coagulant. PS deficiency can be inherited or acquired and predisposes to thrombotic disorders. The inherited type represents an autosomal dominant trait and leads to thrombosis at young age (<40 years) usually without a triggering cause in 50-70% of cases. A family history of thrombosis is present in 50-60% of these cases [2]. Hypercoagulability at high altitude is a well-known entity [3]. We report an unusual case of hereditary PS deficiency with cerebral sinus venous thrombosis (CSVT) and deep vein thrombosis (DVT) occurring at high altitude. We are not aware of previous reports on hereditary PS deficiency with CSVT and DVT occurring at high altitude. However, one case of PC deficiency with CSVT has been reported [4].

Case Report

A 35-year-old male developed severe bifrontal headache, vomiting and drowsiness of sudden onset while located at high altitude (4,572 m). He was inducted into this region following acclimatization, 30 days prior to the onset of his illness. He was a non-smoker with no past history of any medical illness. Neither was there any history of head injury, surgery, seizure or fever. He was evacuated to the plains and clinical examination in a secondary-care hospital revealed a conscious and oriented patient with bilateral papillo-oedema and no signs of meningeal irritation or any other neurological deficit. He was afebrile with a normal blood pressure, pulse and body surface area. There was no icterus, lymphadenopathy or any bleeding manifestation.

Plain CT scans of the brain showed multiple, small, ill-defined areas of hyperdensity in the left parieto-occipital region suggestive of intracerebral haemorrhage. Hb was 16.5 g/dl; haematocrit 50; total WBC count 10×10^9 /l with normal differential count and platelet count of 400×10^9 /l. Blood count values prior to induction were not available. Liver function test, urea, creatinine, electrolytes, blood sugar, chest X-ray and electrocardiogram where found to be normal. Six days later, he developed partial motor seizures involving the right half of the face and right upper and lower limbs. He was treated with valproic acid. On the 9th day, he developed right-sided flaccid hemiplegia with VIIth cranial nerve palsy (right) of upper motor neuron type and bilateral exaggerated deep tendon jerks (right > left) with extensor plantar response.

The patient was treated with intravenous mannitol, Lasix, dexamethasone, broad-spectrum antibiotics and valproic acid was continued. On the 16th day, he was transferred to our hospital, a tertiary-care center where evaluation confirmed the abovenoted neurological findings. In addition, he developed painful swelling of his right leg and thigh. Examination suggested possibility of DVT, which was later confirmed by color Doppler study (popliteo-femoral thrombus) without any evidence of pulmonary thrombo-embolism.

A CT scan of the brain at this time showed evidence of a hyperdense left sigmoid sinus, associated with a haemorrhagic venous infarct. MRI was also performed. The T₁- and T₂-weighted spin echo MRI sequences revealed hyperintensity in the superior sagittal, left lateral and left sigmoid sinuses. An MR venogram revealed lack of flow in the above sinuses with prominent superficial cerebral veins (fig. 1). There was evidence of a large area of altered signal intensity in the parieto-occipital region on the left side, which was hyperintense on T₂-weighted imaging with subacute haemorrhagic areas in it with mass effect. MRI findings were suggestive of thrombosis of the superior sagittal, left lateral and sigmoid sinus with a large venous haemorrhagic infarct in the left parieto-occipital region. The presence of CSVT with peripheral DVT in a young individual with no obvious triggering factor except high altitude necessitated investigations for thrombophilia. The patient was treated with low-molecular-weight heparin for 10 days, overlapping and switching to oral anti-coagulation with warfarin to target an international normalized ratio of 2.5-3.0. His elder brother also had had a stroke at the age of 20 years, but clinical details were not available. There was no history of thrombotic episodes in the parents or two other male siblings. Screening for thrombophilia revealed PS deficiency in this patient with a PS level of 36.50% (normal 70-123%) on functional assay when test-

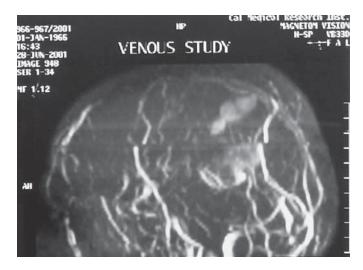


Fig. 1. MR venogram showing lack of flow in superior sagittal, left lateral and sigmoid sinus with prominent superficial cerebral veins.

ed 6 months after the episode, 3 weeks after withdrawal of oral anti-coagulants (warfarin).

Anti-thrombin III and PC levels were normal. Lupus anti-coagulant, anti-cardiolipin antibody and anti-nuclear factor were negative. Prothrombin time, activated partial thromboplastin time and fibrinogen levels were all within normal ranges. Investigations for paroxysmal nocturnal haemoglobinuria including Ham's test, sucrose lysis tests and urinary haemosiderin were negative. Homocysteine levels and echocardiography were normal. There was no evidence of pulmonary arterial hypertension. Following 8 weeks of therapy, the patient made a good recovery, was fully ambulant with normal power in his right upper and lower limbs and was free of seizures. A repeat MR venogram after 1 year (fig. 2a) showed significant improvement in flow through the superior sagittal, left lateral and left sigmoid sinuses, with absent flow only in a short segment of the left sigmoid sinus. An MR venography 66 months later (fig. 2b) showed further improvement with a normal venogram. The patient has been followed up for the last 5 years and is physically asymptomatic. Warfarin was withdrawn 3 years after onset. However, due to recurrence of DVT in the right lower limb, warfarin had to be reintroduced within 8 weeks of withdrawal. The patient made an uneventful recovery and is seizure free on maintenance dose of warfarin to maintain an international normalized ratio of 2.5-3.0.

Discussion

PS deficiency is an established cause for inherited thrombophilia. The term thrombophilia has been used to describe familial or acquired disorders of the haemostatic mechanisms which are likely to predispose to thrombosis [5]. There are no conclusive data on the prevalence of PS deficiency in the general population. To establish

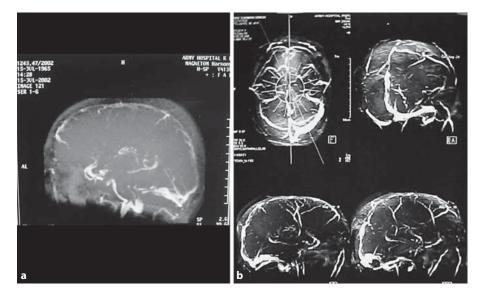


Fig. 2. One year after onset, MR venogram showed significant improvement in flow in the superior sagittal, left lateral and sigmoid sinus with prominent superficial cerebral veins (a) showing a normal venogram 66 months after onset of illness (b).

the inherited form, familial studies are mandatory [1, 3, 4]. However, certain indicators which raise the suspicion of inherited thrombophilia (PS, PC, anti-thrombin III deficiency and activated PC resistance) are thrombotic events at unusual sites (cerebral, mesenteric and upper limbs), often recurrent, occurring at young age (<40 years) with a family history of thrombosis, which is seen in 50–60% of cases [1].

PS deficiency most often leads to spontaneous venous thrombosis and uncommonly to arterial thrombosis. High-risk situations which trigger a thrombotic episode in PS-deficient patients are stasis, trauma, major surgery, co-existing malignancy, oral contraceptives and pregnancy. The likelihood of clinical expression of this deficiency is variable. Almost all kindred have family members who are PS deficient and may be asymptomatic or may have had a single episode of venous thrombosis with or without pulmonary thrombo-embolism. Opinions of haematologists differ on the issue of prophylactic anticoagulation and on the length of anti-coagulation following a documented thrombotic episode [6].

High altitude is defined variably in different studies. Altitude >1,850 m is known to produce acute mountain sickness [7]. Acclimatization is recommended for those proceeding to heights >2,500 m [8]. High altitude is known to cause a hypercoagulable state. Platelet half-life is strikingly reduced and the percentage of circulating young adhesive platelets rises sharply. In combination with increased levels of platelet factor III, factor V and factor VIII, this may result in a hypercoagulable state [9].

Fibrinogen levels tend to fall, indicating a constant depletion due to its conversion to fibrin. Our patient with significantly low levels of PS, when inducted to high altitude, was at a compounded risk to develop a thrombotic event, which resulted in CSVT and DVT of his right popliteo-femoral vein. The inherited nature of PS deficiency was established in our case by family screening. To our knowledge, hereditary PS deficiency with CSVT and DVT occurring at high altitude has not been reported earlier. However, one case of PC deficiency with CSVT has been reported in a mountaineer in the French Alps at an altitude of approximately 3,000 m [4]. In two other reports of CSVT at high altitude involving mountain climbers, investigations for thrombophilia were negative [10, 11]. Hence, ascent to high altitude is an additional prothrombotic risk factor, which is compounded in the presence of hereditary thrombophilia.

Unusual thrombotic episodes, such as CSVT with DVT, warrant a complete investigation for thrombophilia as it has a bearing on anti-coagulation therapy which is often long term in case of life-endangering episodes and recurrent thrombotic events. Prophylactic anti-coagulation is indicated when these patients are faced with any of the high-risk situations noted above.

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