CASE REPORT

PAI-1 polymorphism as a cause of severe high altitude associated arteriovenous thrombosis

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SUMMARY

We present a 34-year-old man who developed disseminated intra-arterial and venous thrombosis following exposure to extreme high altitude. On evaluation, the patient was found to have thrombosis involving the aorta, bilateral iliac arteries and middle cerebral artery. On detailed evaluation for the cause of recurrent seizures, he was also found to have cerebral venous thrombosis of the superior sagittal sinus. The patient underwent amputation of 3 limbs due to gangrene. Procoagulant work up revealed increased plasminogen activator inhibitor-1 activity with 4G/4G polymorphism. This case highlights the life-threatening and limb-threatening thrombosis secondary to a rare inherited thrombophilia on exposure to extreme high altitude.

BACKGROUND

Vascular thrombosis is a major but under-recognised peril of high altitude exposure. There are multiple case reports of pulmonary embolism, renal artery/vein occlusion, cerebrovascular accidents on exposure to high altitude.¹ There are a very few case series or randomised trials that report the exact aetiopathogenesis of thrombosis. Among the various plausible explanations for causation, the important mechanisms include various extrinsic factors such as dehydration leading to haemoconcentration, exposure to extreme cold leading to activation of the coagulation system, restricted movements and constrictive clothing causing venous stasis. The role of inherited thrombophilias was postulated as an aetiological agent in several case reports, commonest being protein C/S deficiencies.² plasminogen activator inhibitor (PAI) mutations have been implicated as a risk factor for venous and arterial thrombosis,^{3–7} but the role of this rare prothrombotic state has never been reported as a cause of high altitude thrombosis. We report one such case of increased PAI-1 activity secondary to 4G/4G polymorphism leading to arterial and venous thrombosis at multiple sites requiring intensive life support and amputation of three limbs.

CASE PRESENTATION

A 34-year-old apparently normal man with no previous comorbidities ascended gradually to an extremely high altitude of 21 000 ft after gradual and strict acclimatisation. He developed pain in the abdomen on 6 February 2005 after staying for 1.5 months at this altitude (since 16 December 2004). The pain in the abdomen was continuous,

diffuse, non-radiating and was not associated with any genitourinary and gastrointestinal symptoms. The patient was managed with supportive care (non-steroidal anti-inflammatory drugs) and rest as he could not be evacuated due to inclement weather. On 10 February 2005, the patient developed weakness of left upper and lower limbs followed by right upper limb weakness. He still could not be retrieved from this altitude due to hostile weather for over 2 weeks. His condition kept deteriorating in the absence of appropriate medical care leading to altered sensorium and seizures. Finally, he was evacuated to a tertiary care centre on 21 February 2005.

On evaluation of the patient at the tertiary care centre, he was averagely built and nourished (height 165 cm, weight 60 kg and body mass index 24.5 kg/m²). His pulse rate was 110/min with a blood pressure of 90/40 mm Hg. He had evidence of left upper and both lower limb dry gangrene. The patient was comatose with bilateral mute plantars.

INVESTIGATIONS

Doppler studies revealed thrombosis of distal aorta, complete occlusion of right and left common iliac artery. Non-contrast CT of the head showed right middle cerebral artery (MCA) infarct with luxury perfusion. MR angiography showed superior sagittal sinus thrombosis with right-sided infarct in the MCA territory. Ultrasound scan of the abdomen revealed portal vein thrombosis. He had evidence of acute renal failure (urea 212, creatinine 7.4) and acute hepatitis (bilirubin 2.4, aspartate transaminase 324, alanine transaminase 218).

DIFFERENTIAL DIAGNOSIS

In an individual with thrombosis at multiple sites the primary differentials considered were diffuse atherosclerosis, thrombotic disease and vasculitis. Angiography of the affected limbs showed diffuse thrombosis with no evidence of atherosclerosis. The patient had undergone a detailed medical evaluation including lipid profile, routine biochemistry (hepatic and liver functions) and cardiac evaluation to rule out any pre-existing comorbidities prior to induction to high altitude, with similar evaluation at regular intervals preceding every stage of ascent. Also, there was no history of dyslipidaemia or hypertension to suggest atherosclerotic disease. Considering a possibility of the thromboembolic disease he was subjected to echocardiography which was essentially normal with a left ventricular ejection fraction of 60% with normal

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valves/chamber dimensions and no evidence of thrombus/vegetations. Serological evaluation including antinuclear antibody (ANA), double-stranded DNA, c-anti-neutrophil cytoplasmic antibody (ANCA) and p-ANCA were negative, imaging and histopathological examination of the amputated limbs did not reveal any evidence of vasculitis. A possibility of inherited thrombophilia versus haemoglobinopathy was considered. High-performance liquid chromatography did not reveal any evidence of haemoglobinopathy. Details of thrombophilia evaluation are enumerated in table 1. PAI-1 activity was increased for which gene polymorphism analysis by allele-specific PCR revealed a 4G/4G homozygous pattern suggesting inherited thrombophilia as the cause of extensive thrombosis.

TREATMENT

The patient was managed with aggressive supportive care and intravenous fluid resuscitation. For mesenteric artery thrombosis, he underwent extensive ileal resection with ileoileal anastomosis. He was also diagnosed to have acute tubular necrosis secondary to muscle necrosis and rhabdomyolysis. On 6 March 2005, he underwent right hip disarticulation, left forearm amputation and left below knee amputation. He also had recurrent generalised seizures on 11 and 12 March 2005 for which he was started on antiepileptic drugs. Subsequently on 21 May 2005 he was given artificial prosthesis after which he was ambulatory. He was initially managed with low molecular weight heparin—enoxaparin (Clexane) 60 mg every 12 hours followed by oral anticoagulants (Acitrom) with international normalised ratio (INR) in the therapeutic range.

OUTCOME AND FOLLOW-UP

The patient is presently asymptomatic with no recurrence of similar symptoms thereafter. His antiepileptics were stopped after 2 years of seizure-free period. He has been kept under continuous observation for past 10 years. His anticoagulation was stopped after a period of 3 years. There has been no recurrence of any arterial or venous thrombosis after stopping anticoagulation. Local examination of the amputated limbs revealed well-healed stumps with no local tenderness and the movement of proximal joints being fully and complete.

Table 1 Results of thrombophilia evaluation in the index case

<i>Thrombophilia evaluation with negative results</i>			
PT	15.0/13.0 (test/control)	Protein C	104% (normal)
aPTT	39.0/32.5 (test/control)	Protein S	110% (normal)
INR	1.09	Antithrombin III	79% (normal)
D-dimer	0.22 µg/mL (normal)	fVL mutation	Not detected
Factor VIII levels	Normal	MTHFR	Heterozygous
Factor IX levels	Normal	JAK2 mutation	Not detected
Serum homocysteine	Normal	EPCR23 mutation	Not detected
PNH	No clone on MFC		
<i>Thrombophilia evaluation with positive results</i>			
PAI polymorphism	Allele-specific PCR	4G/4G homozygous	Positive

aPTT, activated partial thromboplastin time; EPCR, endothelial protein C receptor mutation; fVL, factor V Leiden; INR, international normalised ratio; JAK, Janus kinase mutation; MFC, multicentre flow cytometry; MTHFR, methylenetetrahydrofolate reductase; PAI, plasminogen activator inhibitor; PNH, paroxysmal nocturnal haemoglobinuria; PT, prothrombin time.

Investigations currently carried out revealed a normal haemogram (haemoglobin 15.5 g/dL, total leucocyte count (TLC) $6.4 \times 10^9/L$ and platelet $230 \times 10^9/L$). Renal and liver function tests were within normal limits. Prothrombin time, INR and D-dimer were also within normal limits. Colour Doppler scan showed common carotid artery (CCA), internal carotid artery (ICA) and vertebrals were normal in outline and intimal thickness with no stenosis/occlusion. Bilaterally internal jugular vein is normal. Abdominal aorta and iliac artery/veins were normal in calibre and outline on the left side but attenuated on right side till stump. On left side flow is normal till distal superficial femoral artery (SFA) and stump. The arterial flow was normal in right upper limb/veins and normal on left side till stump. MRI brain, MR venography and MR angiogram showed chronic infarct in the right MCA territory with recanalisation of superior sagittal sinus.

DISCUSSION

Effects of high altitude on coagulation and platelet function is an area of debate owing to increased rate of thrombosis in individuals exposed to high and extreme altitude for prolonged periods.^{1 8 9} The plausible aetiopathogenesis of thrombosis in high altitude could be multifactorial. First, the high altitude per se could lead to increased coagulation and platelet activation by altered expression of platelet proteins and calpain activity.^{10–12} Second, various factors such as immobility at high altitude, dehydration¹³ due to a dry environment and tight clothing leading to stasis have been proposed as causes for thrombosis, with no prospective studies showing the cause–effect relation between the same.⁸ Finally, conditions such as polycythaemia, haemoglobinopathies, inherited thrombophilic states and acquired thrombophilia (oral contraceptives) can lead to thrombosis when exposure to high altitude acts as a second/double hit.

Abnormalities of fibrinolysis are least implicated in the aetiopathogenesis of thrombophilia. Investigation of these abnormalities is very challenging as the routine coagulation assays poorly reflect fibrinolysis. The literature is divided associating abnormal fibrinolysis to thrombophilias. Thrombophilic assays for these abnormalities include testing for levels of tissue plasminogen activator (tPA) antigen, plasminogen, PAI-1 and thrombin activatable fibrinolysis inhibitor. PAI-1 is the principal inhibitor of tPA, the increased level of which leads to hypofibrinolysis. Sartori *et al*⁴ have shown that the patients with PAI-1 4G/4G genotype polymorphism have higher PAI-1 expression and a greater risk of deep vein thrombosis (OR 2.85). Wang *et al*¹⁴ have implicated this gene polymorphism in increased glomerular thrombosis leading to extensive necrotising lesions in patients with lupus nephritis. Glueck *et al*¹⁵ have implicated homozygous gene polymorphism for pregnancy complications secondary to thrombotic placental insufficiency in a stepwise logistic regression model as an independent, potentially significant

Learning points

- ▶ Abnormalities of fibrinolysis can rarely lead to the life-threatening thrombosis.
- ▶ PAI-1 is the principal inhibitor of tissue plasminogen activator, the increased level of which leads to hypofibrinolysis.
- ▶ PAI-1 4G/4G genotype polymorphism has higher PAI-1 expression and a greater risk of deep vein thrombosis.

reversible cause ($p=0.029$). In contrast, Hoekstra *et al*¹⁶ have published the protective effect of 4G allele against stroke secondary to stabilisation of atherosclerotic plaques because of high tissue PAI.

We presented this case to highlight a rare inherited thrombophilic state leading to life-threatening and limb-threatening thrombosis at extreme high altitude.

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Contributors VN and RK were involved in the initial management of the case. KG conducted a detailed thrombophilia profile continuously over the past 10 years. VN and UY followed up the patient for the past 10 years. VN and UY drafted and approved the manuscript.

Competing interests None declared.

Patient consent Obtained.

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