Cerebrovascular Events in High Altitude: Role of Inherited Prothrombotic Factors

Dr. Saurabh Dawra

INTRODUCTION

Stay at high altitude may predispose to thrombotic cerebrovascular disorders. The role of inherited procoagulant states in predisposing to these events has not been well studied in the Indian subcontinent. With increasing role of Indian soldiers at these heights for long periods and development of adventure tourism in our country, there is a need to study this aspect to establish a basis for risk profile assessment and screening tools for primary prevention of high altitude related strokes and other cerebrovascular events.

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I. INTRODUCTION

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II. MATERIALS AND METHODS

All cases of acute onset focal neurological deficit suggestive of stroke/Transient ischemic attack (TIA)/Intracerebral bleed developed at High Altitude (Ht >9000ft above means sea level), referred for management at a tertiary care Neurology centre during the period Jun 2009 to Jul 2011 were included for study. Patients with past history of stroke/TIA, hypertension, dyslipidemia, coronary artery disease, valvular heart disease (congenital/rheumatic), peripheral arterial disease, diabetes mellitus (DM), malignancy or drug abuse were excluded. After complete clinical evaluation to confirm the diagnosis, patients were subjected to investigations based on a standard protocol including complete blood counts, lipid profile, blood glucose levels, renal and liver function tests, ECG, chest radiograph and echocardiography.

Coagulogram including prothrombin time, activated Partial Thromboplastin time (aPTT) and serum fibrinogen levels were done. Tests for prothrombotic states like platelet aggregation test, protein C & S assay, Anti thrombin III (AT III) assay, Factor V Leiden, antiphospholipid antibodies (APLA) and Serum homocysteine levels was done. Statistical analysis using chi square test and Fisher's exact test was carried out.

III. RESULTS

A total of 66 patients were included in the study. This included 65 males and 01 female. The mean age of patients was 34.2 (± 7.376) yrs (Range 20-51yrs). Most of the patients were young, considering the usual age of soldiers posted at this altitude. Mean duration of stay at HAA was 9 months (range 2wks – 36mths). The vascular events noted included stroke (arterial and venous thrombosis), TIA and intracerebral haemorrhage.

There was no seasonal variation noted in the incidence of the high altitude related cerebrovascular events. Maximum events (36.4%) occurred at altitude more than 18,000 ft. The mean altitude of stay was 15,467 ft (SD ± 3317.36) and ranged from 10,300 ft – 22,000 ft. The altitude wise occurrence of cases is depicted in table 1. The mean duration of stay was 9.89 months and ranged from 0.33 months to 36 months (SD ± 7.00 months).

Total number of cerebrovascular events was 66 which included arterial stroke in 26, venous stroke in 26 and 02 patients suffered from intracerebral haemorrhage. Ten patients had TIA with normal MRI brain and 01 patient had spontaneous subdural haematoma.

A total of 26 patients had an arterial infarct (15 of them under 40yrs of age). Out of these 26 patients, 14 had Left Middle cerebral artery (MCA) infarct (01 patient had extensive Lt MCA + ICA infarct) and 07 patients had Right MCA infarct, 05 had lacunar infarcts and 03 had bilateral non specific ischemic changes. Of the 26 patients who had venous infarcts, 20 patients had associated parenchymal lesion while 06 patients suffered from cerebral venous thrombosis without any parenchymal involvement.

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Mean haemoglobin level was 15.14 (SD ± 1.63) g/dl (range 12.4 – 18.8). Average hematocrit (hct) was 45.20 (SD ± 3.15). Platelet count showed mean of 3,00,000/ul (SD±.71). Co-existing pulmonary thromboembolism occurred in one patient of arterial stroke. Echocardiography was normal in all except the patient with co-existing pulmonary thromboembolism.

IV. PROCOAGULANT WORK UP

Prothrombin time and aPTT was normal in all patients. Out of 66, 55 pts (84%) had one or more underlying inherited procoagulant state. Hyper-homocysteinemia (34) and Protein S deficiency (34) were the commonest defects. Details are tabulated in Table #. Sixteen out of 27 patients with arterial stroke had Protein S deficiency, 13 had hyperhomocysteinemia, 06 had protein C deficiency and 02 had factor V leiden mutation.

Venous strokes were noted in 26 patients with hyperhomocysteinemia in 17, Protein S deficiency in 16 and Protein C deficiency in 4 patients. Antithrombin III deficiency, Lupus anticoagulant, Anti-Cardiolipin antibodies IgM and IgG were not detected in any patient.

V. DISCUSSION

In this study of 66 consecutive patients with cerebrovascular events at high-altitude, despite low baseline risk for such events, we assessed the nature of vascular involvement and underlying hypercoagulable state. Classical risk factors for vascular events like hypertension, DM, dyslipidemia and prior vascular events were excluded in these patients. Altitude of more than 9000ft was defined as HAA as per existing regulations in the Indian Army. Mean duration of stay prior to onset of neurological event was 9 mths and in 40% of patients, the onset was within 6 mths, which is the usual period of stay at altitudes above 15000ft. Eighty percent of events occurred within 1yr of stay which needs to be set as upper limit of tenure at these altitudes. Arterial thrombosis was the commonest cerebrovascular events noted followed by venous thrombosis.

Patients developing venous thrombosis were younger compared to those who had arterial stroke, although statistically insignificant, likely due to atherosclerosis being basic underlying defect in arterial strokes which gets frequent with ageing.

Inherited procoagulant state was detected in 55 (84%) patients. Commonest defects noted were hyperhomocysteinemia and protein S deficiency in both arterial and venous thrombosis. Factor V Leiden mutation was noted in 3 cases, all having arterial strokes.

Similar frequency of underlying inherited procoagulant state was seen in patients with venous thrombosis and those with arterial stroke.

Compared to earlier studies from this region,(1-6) we noted higher frequency of inherited procoagulant states. Erythrocytosis or other classical risk factors for vascular thrombosis were not noted in these patients.

To the best of our knowledge, this is the largest Indian study evaluating the frequency of inherited procoagulant states in young patients with high altitude related cerebrovascular events. (1-6) The Strengths of this study were the sample size, assessment of clinical risk profile and procoagulant state in all cases. A study population, with low risk profile, having increased frequency of cerebrovascular events, was good subset to study the frequency and impact of inherited procoagulant risk factors in these events.

Limitations of this study were its restricted study population involving young males, who were not evaluated for underlying procoagulant state before induction to HAA. There is no data available in the unaffected control population in the same region of these procoagulant factors. Role of exposure to low ambient temperatures and hypoxia in HAA in induction/activation of these procoagulant defects needs further evaluation with a prospective study.

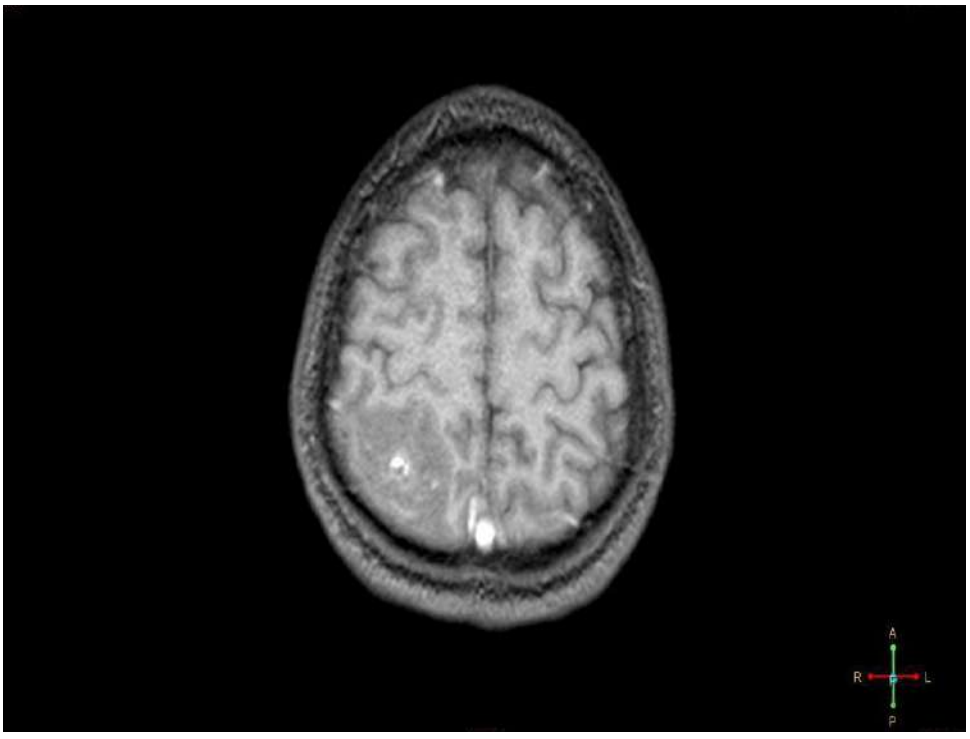
This study highlights the high incidence of cerebrovascular thrombotic events with its devastating effects in otherwise healthy young soldiers posted at HAA. Various inherited procoagulant states noted in these patients may have a significant role to play in pathogenesis of

these events when exposed to HAA, which can only be shown in a prospective study with a healthy control group from the same region. A larger study with a suitable design can address this issue. Pre-induction screening of the inductees to HAA regarding procoagulant states in them may help in risk-stratifying and institution of prophylactic measures like anti-platelets and anticoagulants and decreasing the duration of exposure to these altitudes in high risk cases.

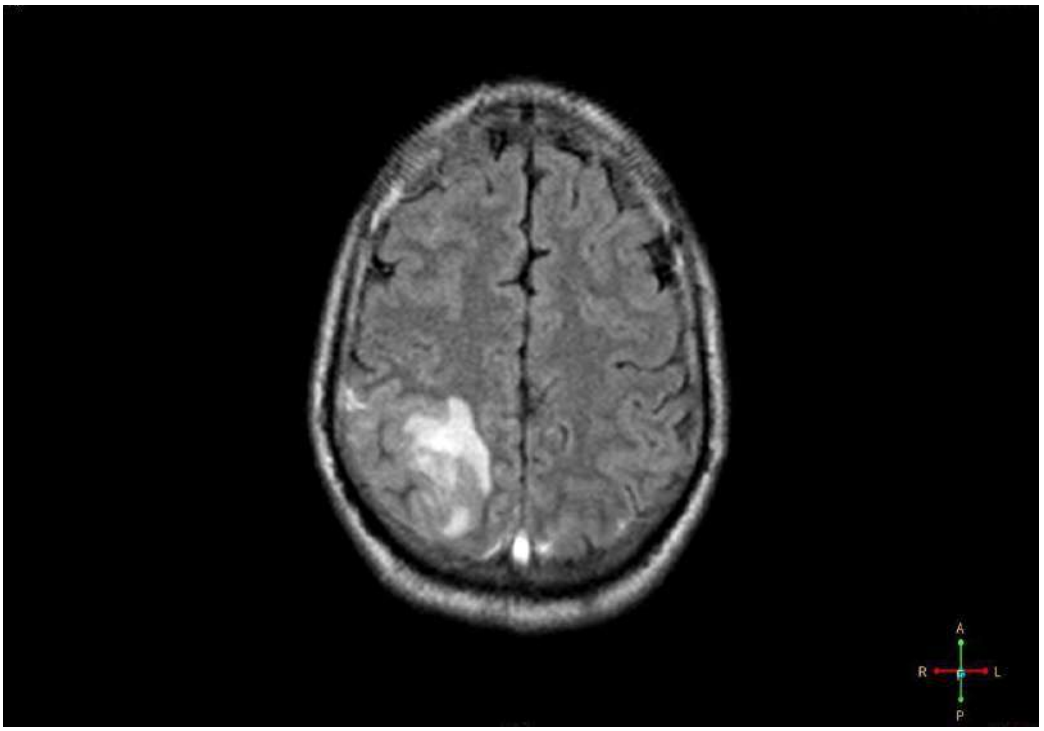
Table 3: Demographic profile of patients with stroke at high altitude area

Characteristics	Patients
Number of patients	66
Age (Years) Mean Range	34.24 21 – 51
Sex Male Female	65 01
Past history of stroke/TIA	00
Family history of Stroke/TIA	00
Duration of stay at high altitude before onset of symptoms Mean Range	 09 months 15 days – 36 months
Altitude of stay Mean Range	 15,467 ft 10,300 – 22,000 ft

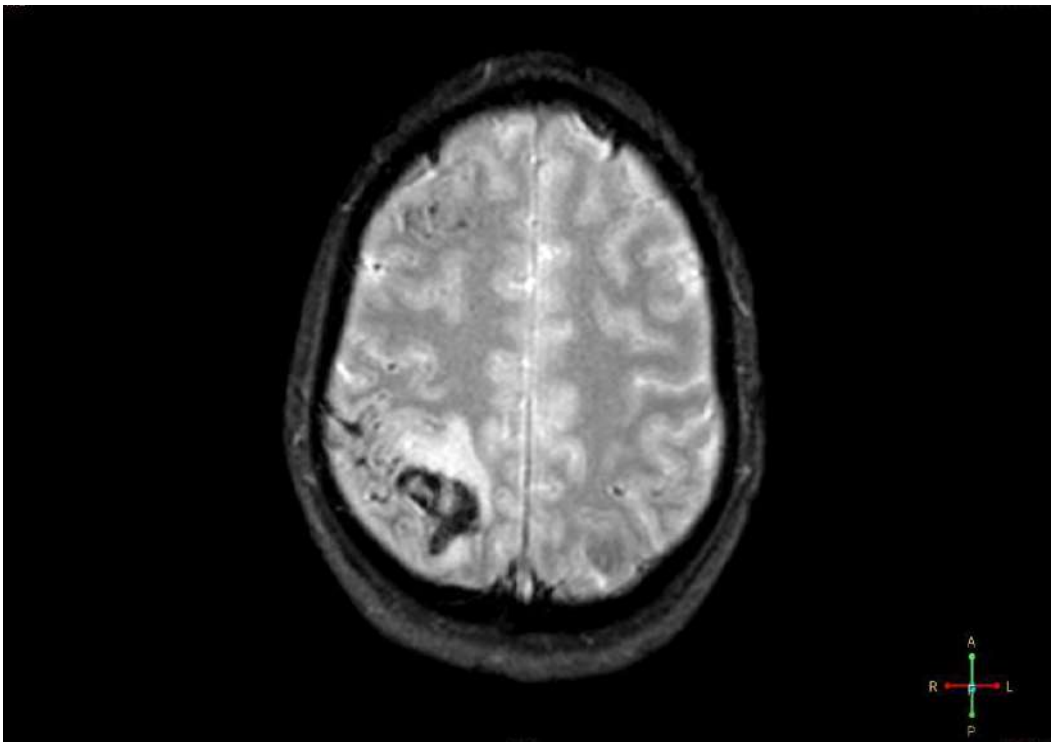
T1 Axial image showing hyperintensity in superior sagittal sinus with a hypointense lesion in the Rt parietal region suggestive of haemorrhagic foci



Fluid attenuated inversion recovery(Flair) Axial image showing hyperintensity in superior sagittal sinus with a hypointense lesion in the Rt parietal region suggestive of haemorrhagic foci



Gradient T2 Fast field echo imaging(FFE) showing blooming on gradient images suggestive of haemorrhage



Magnetic resonance(MR) Venogram showing irregularity, narrowing and absence of flow in the superior sagittal sinus suggestive of superior sagittal sinus thrombosis

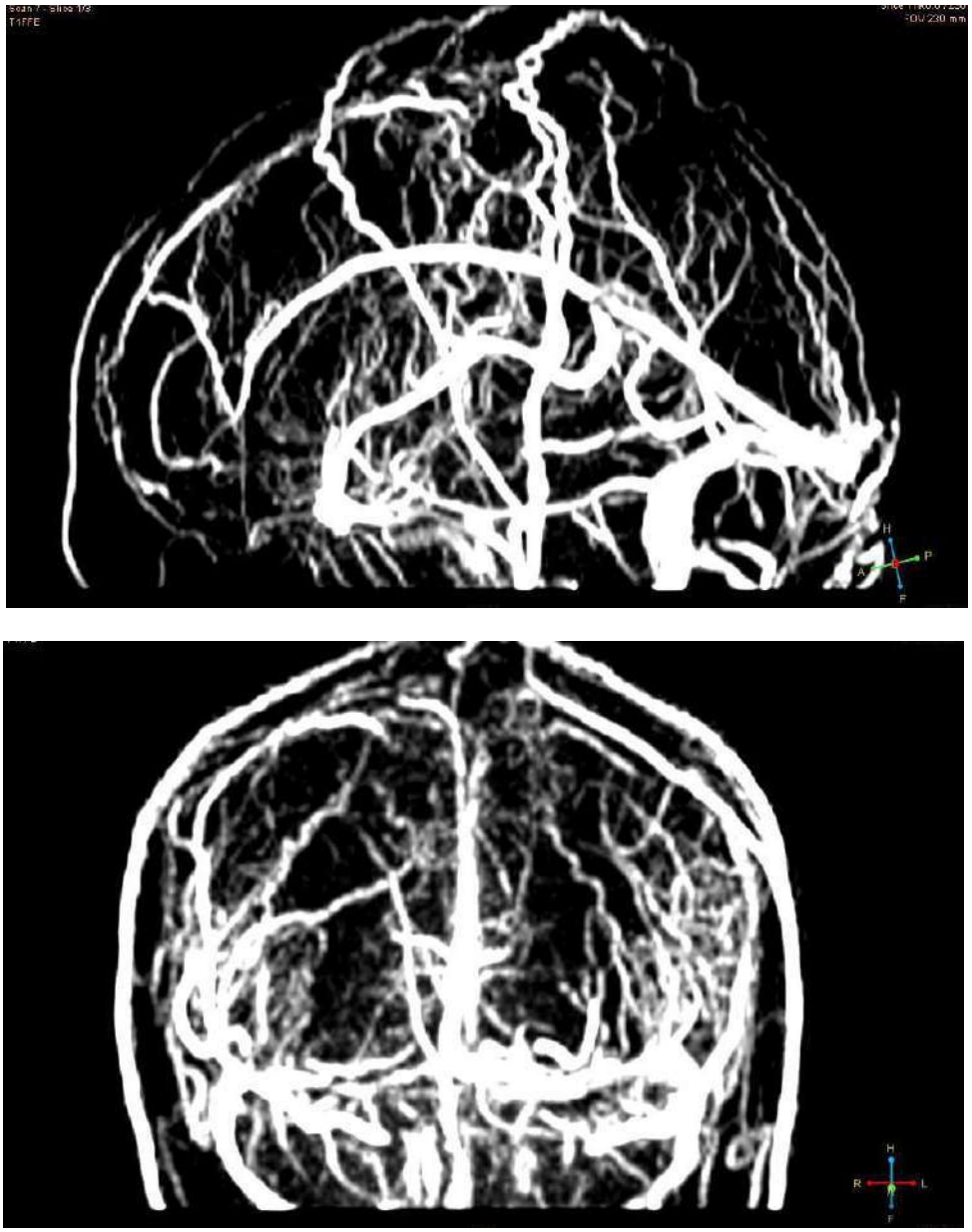


Table 01: Altitude wise distribution of cases of cerebrovascular events in HAA

Height (ft above MSL)	Number of patients	Percentage (%)
> 18,000	24	36.37
15,000 – 17,999	14	21.21
13,000 – 14,999	08	12.12
11,000 – 12,999	20	30.30
9,000 – 10,999	00	00

Table No. 2: Inherited procoagulant state and Cerebrovascular events at HAA

Procoagulant state	Arterial strokes (N=27)	Venous strokes (N=26)	TIA (N=10)	ICH (N=2)	SDH (N=1)	Total (N=66)	P value
Hyper Homocysteinemia (H) only	01	03	01	00	00	05	
Protein C deficiency only (C)	01	00	03	02	00	06	
Protein S deficiency only (S)	06	04	02	00	00	12	
H+C	02	02	03	00	00	07	
H+S	07	10	00	00	00	17	
H+C+S	03	02	00	00	00	05	
Factor V Leiden	02	00	01	00	00	03	
No defect	05	05	00	00	01	11	
Total	27	26	10	02	01	66	

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