

Original Research Article

Stroke in young among exposed to high altitude: prospective observational study in Eastern India

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ABSTRACT

Background: High altitude deployment for longer duration is a usual event among armed forces personnel. Despite our knowledge and understanding about the risk factors and treatment, stroke still remains the second leading cause of death worldwide. Present study was carried out at a teaching hospital in India, where many soldiers from high altitude area in Eastern India were referred for super speciality care. Our objective was to study the various clinical presentations and risk factors in patients of stroke in age group 15-49 years having longer duration of stay at high altitude.

Methods: Patients of stroke between ages 15-49 years, referred to a tertiary care service hospital were treated and evaluated for potential risk factors including prothrombotic factors and analysed using SPSS 15.0.

Results: Mean age of patients of cerebral venous thrombosis (CVT), ischemic and hemorrhagic strokes in high altitude area (HAA) was 31.40, 38.68 and age of 38.60 years respectively. Mean Hemoglobin (Hb), homocysteine, serum protein C and S, and antithrombin III levels of HAA ischemic strokes patient was significantly higher than non high altitude area (NHAA) Patients. In case of CVT the difference in mean Serum protein S level of HAA and NHAA patients was significant. There was no statistical difference observed in mean values of serum homocysteine, protein C, protein S and antithrombin III among ischemic stroke and CVT patients in HAA.

Conclusions: Prothrombotic state in case of CVT and ischemic strokes is an important risk factor in case for strokes among young individuals in HAA.

Keywords: High Altitude, Prothrombotic factors, Polycythemia, Stroke

INTRODUCTION

High altitude employment for longer duration is a usual event among armed forces personnel. The adverse environmental conditions and the associated hypobaric hypoxia at high altitude remains a tuff physiologic challenge to the soldiers. However, hypoxia or high altitude exposure are still not established as potential risk factor for development of stroke as presence of various possible factors like duration of stay at high altitude, previous risk factors and genetic factors are difficult to

control.¹ Despite our knowledge and understanding about the risk factors and treatment, stroke still remains the second leading cause of death worldwide.¹ According to WHO, stroke and ischemic heart disease accounted for a combined 15 million deaths in 2015, more than two third occurring in less developed countries.²

Most of the available literature on the subject is based on studies conducted on armed forces soldiers, particularly Indian. A study on Indian soldiers has suggested that prolonged stay in high altitude area may lead to

hypercoagulable state.³ Polycythemia, increase in platelet adhesiveness and increased risk of developing thrombosis, coupled with other conditions like dehydration, extreme cold climate and forced immobilization due to extreme weather conditions have been identified as risk factors for stroke among high altitude dwellers.¹ Raised hemoglobin (Hb) found in another study on Indian soldiers has also been incriminated as contributing factor.⁴ Longer stay and moderate and extreme altitude carries 30 times higher risk of developing vascular thrombosis.⁵ In a study conducted at a tertiary care armed forces hospital, stroke constituted 13.7/1000 admission between November 1998 to July 2000, all patients were male soldiers having mean stay at high altitude as 10.2 months, and mean age 33.4 years.⁴

Present study was carried out at a teaching hospital in India, where many soldiers from high altitude area (HAA) in Eastern India were referred for super specialty care, besides other patients of “stroke in young” from non high altitude area (NHAA). In this study, we managed young patients of stroke between 2010-2014 and investigated patients for presence of thrombophilic states, which are disorders of hemostatic mechanisms, that result in a predisposition to thrombosis. During study period a total of 144 patients aged 15-49 years of age were included in the study, 53 patients developing stroke while in high altitude were aggressively managed and investigated for possible aetiological factors. Objective of study was to study the various clinical presentations and risk factors in patients of stroke in age group 15-49 years having more than 3 months of stay at HAA.

METHODS

This is a prospective observational study. Study population involves patients of stroke between ages 15-49 years, who reported to Outpatient Neurology Services or admitted to a teaching hospital in a metropolitan city in Eastern India, from 31 May 2010 to 30 June 2014.

The proposed sample size of 81 was based on average incidence of 16% of stroke in young adults in India,⁶ and considering alpha error of 5% and error value of 8% on either side, However, 144 patients presented to study hospital during study period were included in the study, 53 of them had been referred from high altitude.

Inclusion criteria

Patients with first ever stroke (ischemic or hemorrhagic or cerebral venous thrombosis) in age group 15-49 years.

Exclusion criteria

Stroke patients <15 years and >49 years of age, recurrent strokes, and transient ischemic attack were excluded from study.

Study protocol

All cases underwent detailed history taking, clinical examination, baseline investigations, and specific investigations including prothrombotic workup were carried out on basis of initial presentation and findings of baseline investigations. Alcohol consumption was taken as significant when an individual consumed more than 70 gm of alcohol in females and 140 gm in males per week. Smoker was defined as an individual who had smoked greater than 100 cigarettes in their life time and currently smoking prior to event. Upper level of normal blood pressure was taken as 140/90 mm of Hg. High altitude area (HAA) was defined as area at height more than 9,000 feet above the sea level and minimum stay of 3 months was taken to qualify for resident of HAA. Prothrombotic factors (Homocysteine (normal values 5.46-16.2 μ mol/l), protein S functional (normal values 70-140 %), protein C functional (normal values range between 73-143%). Antithrombin III (normal values range between 80-120%), factor V Leiden mutation analysis, Antiphospholipid antibodies panel (IgG, IgM) in serum (antibodies are found at a level between 0.50-10 MPL U/ml for IgM and 0.50-10 GPL U/ml for IgG.) were assayed in all cases of cerebral venous thrombosis (CVT) and in cases of ischemic strokes without hypertension and diabetes mellitus.

Analysis of data

All raw data were analysed using standard statistical software, SPSS15.0. Continuous numerical data was described as means, standard deviations, medians, minimum, maximum and standard error of mean. Further, mean was compared across 3 groups by ANOVA test, distributions were compared using Pearson's Chi Square Test. Two-sided values of $p < 0.05$ were considered statistically significant.

RESULTS

Among 144 patients treated during the period of study, residence at HAA was present in 10 (38%) cases of CVT, 38 (38.4%) cases of ischemic strokes and in 5 (26.3%) cases of hemorrhagic strokes (Table 1). However residence at HAA was not an important risk factor in respect of any type of stroke whether CVT, hemorrhagic or ischemic strokes (p value 0.596). Among all case of ‘Stroke in Young in high altitude’ 71% cases were of ischemic, and 18.87% and 9.43% of haemorrhagic and CVT respectively.

Age

CVT occurred in younger age group with mean age of 31.40 years as compared to ischemic strokes with mean age of 38.68 and hemorrhagic strokes with mean age of 38.60 years. (Table 2) The difference in age between different groups is statistically significant ($p=0.015$).

Table 1: Stroke among Young in HAA versus NHAA.

		HAA		Total
		NHAA (%)	HAA (%)	
Type	CVT	16 (61.54)	10 (38.46)	26 (18.06)
	Hemorrhagic strokes	14 (73.68)	5 (26.32)	19 (13.19)
	Ischemic strokes	61 (61.62)	38 (38.38)	99 (68.75)
Total		91 (100)	53 (100)	144 (100)

Table 2: Profile of patients of “stroke in young” among HAA.

Parameters	CVT	Ischemic stroke	Haemorrhagic stroke
Mean age (95% CI)	31.40 (27.21-35.58)	38.68 (36.49-40.87)	38.60 (30.81-46.38)
Sex (M:F)	10:0	38:0	5:0
Consumes alcohol N (%)	5 (50.00)	25 (65.78)	4 (80.00)
Smokers N (%)	2 (20.00)	14 (36.84)	0 (0)
Presence of hypertension N (%)	0 (0)	11(28.95)	2 (40.00)
Presence of diabetes mellitus N (%)	0 (0)	2 (5.26)	0 (0)
Mortality (n)	1	1	0

Sex

All patients from high altitude were male patients only.

Alcohol and smoking

Among HAA patient’s alcohol consumption was found in 25 (65.79), 4 (80%) and 5 (50%) in ischemic, haemorrhagic and CVT respectively (Table 2). Among NHAA patient’s alcohol consumption was found in 33 (55.93), 7 (50%) and 10 (62.5%) in ischemic, haemorrhagic and CVT respectively. Consumption of alcohol was significantly higher in NHAA group among CVT patients (p=0.03156).

Among HAA patients smoking was found in 14 (36.84), 0 (0%) and 2 (20%) in ischemic, haemorrhagic and CVT

respectively (Table 2). Among NHAA patients smoking was found in 13 (22.03), 3 (21.43%) and 0 (0%) in ischemic, haemorrhagic and CVT respectively. The difference between HAA and NHAA in any type of stroke was not significant.

Symptomatology

CVT presented as headache in 9 (90%) cases, which was the commonest presentation followed by vomiting, (Figure 1) whereas hemiplegia in cases was the most common presentation in Ischaemic stroke (84.21%) (Figure 2). Hemorrhagic strokes presented as hemiplegia in 4 (80%) cases along with associated facial weakness in 3 (60%) cases; vomiting and headache each in 3(60%) cases, and 2 (40%) cases had altered sensorium at presentation (Figure 3).

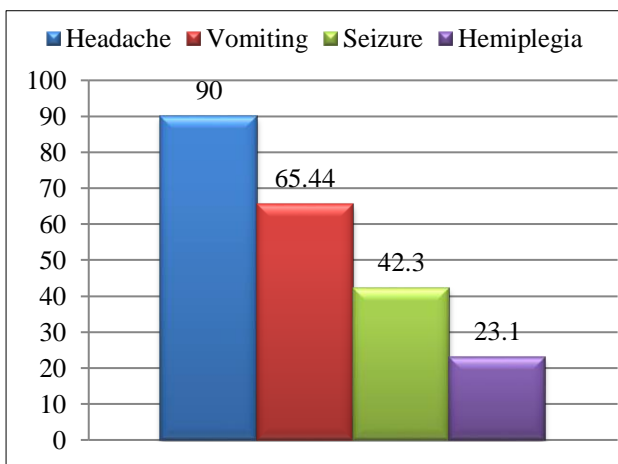


Figure 1: Commonest presentation of CVT (in percentage).

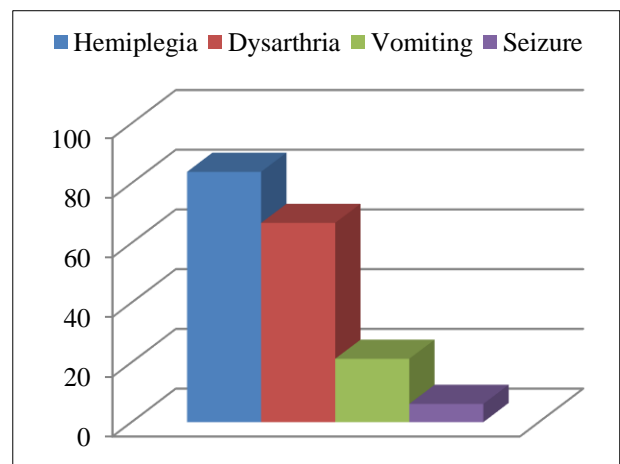


Figure 2: Commonest presentation of ischaemic stroke CVT (in percentage).

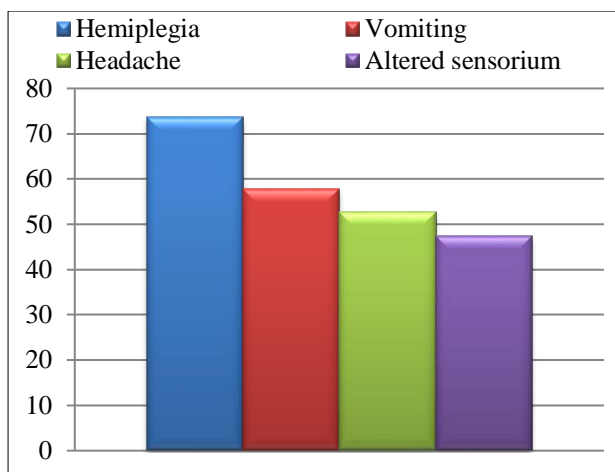


Figure 1: Commonest presentation of haemorrhagic stroke.

Hb

Lower level of hemoglobin was found in cases of hemorrhagic strokes with mean Hb level being 12.84 gm/dl (95% CI 11.56-14.11) as compared to ischemic strokes (mean Hb level 14.42 95% CI 13.86-14.96 gm/dl) and CVT (mean Hb level 13.74, 95% CI 12.39-15.08 gm/dl). Lower values are associated with hemorrhagic strokes. Also, higher values of Hb are associated with ischemic strokes as compared to CVT. However, the difference in mean Hb between these groups was not statistically significant (p=0.137). The difference in mean Hb level of HAA ischemic strokes patients was statistically significantly higher than NHAA Patients (95% CI -1.77 to -0.38) (Table 3).

Platelets

Mean platelets level in case of ischemic strokes was 2.42 (95%CI 2.15-2.69) lacs per mm³, while in case of CVT it was 2.15 (95%CI 1.65-2.64) lacs per mm³ and 2.21 (95%CI 1.29 -3.11) lacs per mm³ in cases of hemorrhagic strokes (Table 3). No significant differences were observed in case of platelets level amongst different types of strokes. The difference between high altitude and other patients also for all three types of stroke was not significant.

Prothrombotic state

Amongst 38 cases of ischemic strokes in HAA, prothrombotic state was investigated in 24 cases (excluding 11 cases with classical risk factors like diabetes mellitus and hypertension, two patients died and one was unwilling for investigation).

In cases of ischemic stroke, Hyperhomocysteinemia was found in 15 (62.2%) cases. The difference in mean homocysteine level of HAA and NHAA patients was significant (95%CI 1.23-13.78) (Table 3). Serum protein S deficiency state was detected in 21 (87.5%) cases, the difference in mean serum protein S level of HAA and NHAA patients was significant (95%CI 3.25-27.78). Serum protein C deficiency state in 5 (20.8%) and antithrombin III deficiency was found in 9 (37.5%) cases of ischaemic stroke. The difference in mean antithrombin III level of HAA and NHAA patients was statistically significant (95%CI 1.81-40.70). While factor V Leiden mutation was detected in 2 (8.33%) cases, multiple prothrombotic states were detected in 12 (50%) cases and none was found to have antiphospholipid antibodies in cases of ischemic strokes.

Table 3: Prothrombotic factors and other variables among HAA and NHAA patients.

Variable		High altitude			Low altitude			SE	95%CI
		N	Mean	SD	N	Mean	SD		
Age	CVT	10	31.4	6.75	16	33.25	7.45	2.90	-4.13 to 7.83
	Haemorrhagic	5	38.6	8.87	14	41.85	5.94	3.514	-4.16 to 10.66
	Ischemic	38	38.68	6.89	59	40.81	5.96	1.318	-0.48 to 4.74
Hb (gm/dl)	CVT	10	13.74	2.16	16	14.37	0.95	0.613	-0.63 to 1.89
	Haemorrhagic	5	12.84	1.45	14	12.87	2.13	1.037	-2.15 to 2.12
	Ischemic	38	14.42	1.71	59	13.34	1.71	0.353	-1.77 to -0.38
Platelet (lacs/mm ³)	CVT	10	2.15	0.79	16	2.02	0.74	0.306	-0.76 to 0.50
	Haemorrhagic	5	2.21	1.04	14	2.06	0.51	0.351	-0.89 to 0.59
	Ischemic	38	2.42	0.85	59	2.22	0.67	0.157	-0.51 to 0.11
Serum homocysteine	CVT	9	21.82	6.93	15	32.90	23.78	8.190	5.90 to 28.06
	Ischemic	24	18.30	7.26	27	25.81	13.68	3.124	1.23 to 13.78
Protein C	CVT	9	81.43	37.43	15	106.92	32.24	14.42	4.43 to 55.41
	Ischemic	24	94.13	24.81	27	94.18	24.86	6.968	-13.95 to 14.05
Protein S	CVT	9	39.33	22.94	14	63.38	22.03	9.562	4.16 to 43.93
	Ischemic	24	51.18	22.46	27	66.7	21.11	6.103	3.25 to 27.78
Antithrombin III	CVT	9	97.38	26.81	13	109.29	18.22	9.566	-7.94 to 31.96
	Ischemic	24	72.5	46.77	27	93.76	17.54	9.678	1.81 to 40.70

In case of CVT, prothrombotic state was investigated in 9 out of 10 cases (1 patient had died). Hyperhomocysteinemia was found in 8 (88.88%) cases, serum protein S deficiency state was detected in 8 (88.88%) cases, serum protein C deficiency state was found in 5 (55.5%) cases and antithrombin III deficiency was found in 1 (11.11%) cases. Factor V Leiden mutation was detected in 2 (22.22%) cases, multiple prothrombotic states were detected in 6 (66.66%) cases and none was found to have antiphospholipid antibodies in cases of CVT. (Table 3). The difference in mean Serum protein S level of HAA and NHAA patients was significant (95%CI 4.16-43.93). There was no statistical difference observed in mean values of serum homocysteine, protein C, protein S and antithrombin III among ischemic stroke and CVT patients in HAA (Table 3).

Higher level of serum homocysteine was associated with CVT (21.82 $\mu\text{mol/l}$) than ischemic strokes (18.30 $\mu\text{mol/l}$). It is not statistically significant when comparison is done between ischemic strokes and CVT (95%CI -9.24 to 2.20) (Table 3).

In CVT more patients had factor V Leiden mutation (22.22%) as compared to ischemic strokes (8.33%). It is not statistically significant when comparison is done between ischemic strokes and CVT ($p=0.462$).

In CVT lower values of protein S was found (39.33, 95%CI 24.32-54.32) as compared to ischemic strokes (51.18, 95%CI 42.19-60.16), but more patients had protein S deficiency state in case of CVT (88.88%) as compared to ischemic stroke group (87.5%). It is not statistically significant when comparison is done between ischemic strokes and CVT (95%CI -6.15 to 29.85) (Table 3).

In CVT group, protein C levels were 81.43 % and in ischemic group levels were 94.13. Higher percentage of patients with protein C deficiency state was found in CVT (55.5%) as compared to ischemic strokes (20.8%). It is not statistically significant when comparison is done between ischemic strokes and CVT (95%CI -10.10 to 35.50) (Table 3).

Lower values of antithrombin III were found in ischemic strokes (72.5) as compared to CVT (97.38). ATIII deficiency state was predominantly seen in cases of ischemic strokes (37.5%) as compared to CVT (11.11%). It is not statistically significant when comparison is done between ischemic and CVT (95%CI -58.78 to 9.02) (Table 3).

Antiphospholipid antibody was found to be negative in all cases of CVT and ischemic strokes.

DISCUSSION

lower value of hemoglobin levels were found in hemorrhagic strokes as compared to ischemic strokes and

CVT, although the difference was not statistically significant ($p=0.137$). However, mean Hb among ischemic stroke patients of HAA was significantly higher than ischemic stroke patients of NHAA ($p=0.137$). Previous studies also showed that anaemia was significant risk factors for strokes in young.⁶

Higher values of haemoglobin were associated with ischemic as compared to CVT and hemorrhagic strokes. Polycythemia has been identified as potential risk factor for ischemic stroke.^{1,4,7} It is well known that haematocrit and Hb level increases exponentially with altitude, thus increasing the viscosity of blood and risk of cerebral infarction. However, incidence of stroke at moderate altitude was found lower than low altitude in a study done at a tertiary care hospital in Himachal Pradesh state of India.⁸

Significant numbers of HAA patients without the classical cardiovascular risk factors had prothrombotic states in case of CVT and ischemic strokes indicating that these are important risk factors for strokes in young in India. This is supported by various studies done in past on stroke in young population.^{1,4,6,7,9-11} In this study hypertension was present in 23.68% cases of ischemic stroke and 40% of CVT at HAA and 33.9% among ischemic stroke and none in CVT in patients at NHAA. The incidence of hypertension is less than a study of stroke at moderate altitude but more than a clinic haematological study of 21 cases.^{8,12}

High levels of homocysteine were present in 80% cases of CVT and in 62.5% cases of ischemic strokes in HAA. Workshop over stroke by ICMR in 2006 supported by WHO also stated that 54.6% of patients of stroke in younger population had high levels of homocysteine in Guwahati stroke registry.⁶ Though another study from Pakistan found only 4% cases due to miscellaneous causes including hyperhomocysteinemia.¹³ Another case control study from India reported high homocysteinemia in 14.28%.¹² Hyperhomocysteinemia coupled with high altitude is a significant risk factor for "stroke in young".

Present study found protein S deficiency states in 87.5% cases of ischemic strokes as compared to 80% cases of CVT, whereas previous studies showed that isolated protein S deficiency state may be seen in only 10% of cases of young ischemic strokes.¹⁴ Lee et al, found 6.8% cases of young ischemic strokes had protein S deficiency state and Indian case control study has reported only 4.76%.^{11,12} Another Indian study from Chandigarh has reported only 3.33% cases of protein S deficiency.⁴

In this study, it was found that protein C deficiency states in 20.8% cases of ischemic strokes as compared to 50% cases of CVT, whereas study by Nedeltchev et al, noted only 0.5% incidence of protein C deficiency state in cases of young ischemic strokes.^{4,5} Lee et al, found 2.5% cases of young ischemic strokes had protein C deficiency state and Indian case control study has reported only

4.76%.^{12,13} Another Indian study from Chandigarh has reported only 3.33% cases of protein C deficiency.⁴

Authors found antithrombin III deficiency states in 37.5% cases of ischemic strokes as compared to 10% cases of CVT. Lee et al, found 1.9% cases of young ischemic strokes had antithrombin III deficiency states.¹¹ The deficiency of antithrombin III after 8 months of induction to HAA was significantly different from level at the time of induction.¹⁵ The deficiency in patients from LHAA in our study was 18.51% in ischemic stroke patients and 7.69% in CVT.

In this study, factor V Leiden mutation was found in 5.26% cases of ischemic strokes as compared to 20% cases of CVT, whereas Nedeltchev et al, noted 0.9% incidence of factor V Leiden mutation in cases of young ischemic strokes.³ Also two stroke centres based studies found 0.9% cases of young ischemic strokes had factor V Leiden mutation.¹⁶

Multiple thrombotic factors were present in 50% cases of ischemic and 60% of CVT at HAA while 18.57% in ischemic and 60% in CVT among patients from NHAA. Stroke is leading cause of mortality worldwide responsible for more than 6 million lives each year.¹⁶ The disease assumes paramount socio-economic importance among young since the families are devastated by stroke of the breadwinner of family.¹⁷

CONCLUSION

Significant proportion of patients had prothrombotic states in case of CVT and ischemic strokes indicating that it is an important risk factor in case of young patient of strokes.

A large proportion of patients of ischemic stroke without classical cardiovascular risk factors were found to have pro thrombotic state like hyperhomocysteinemia and protein S followed by protein C deficiency states. A similar association was found with CVT.

Authors findings are in contrast to previous studies, hence further studies are required to establish the fact.

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