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Increased Incidence of Intracerebral Haemorrhage in winter in India - a Prospective Study

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I. Introduction

Cerebrovascular diseases or stroke broadly can be classified into ischemic (85%) and haemorrhagic (15%) types. The incidence of cerebrovascular diseases increases with age and the number of strokes is projected to increase as the elderly population grows, with a doubling in stroke deaths [1].

Stroke is the third largest cause of mortality in India after heart attack and cancer [2]. Reliable morbidity and mortality estimates for stroke in India are limited due to incomplete death certification, classification, and uncertainty of aetiology in cases of sudden death or multiple co morbidities [3]. The crude prevalence rates have shown significant regional variation.Age adjusted prevalence rate for stroke is estimated to lie between 84-262/100,000 in rural and between 334-424/100,000 in urban areas [4]. Several studies from different countries and climatic zones have demonstrated a seasonal variation in morbidity and cerebrovascular disease (CVA), but the findings had many discrepancies making the conclusion unclear [5]. The inconsistency occurred due to small sample size and most of the studies did not analyze the subtypes of strokes. **A** winter excess of ischaemic stroke in hospital-based studies is often assumed to be due to seasonal variation in stroke and several pathophysiological explanations have been proposed in this favour. Lower temperatures in winter are associated with more mortality than in the summer mostly due to cardiovascular and cerebrovascular events related to blood pressure (BP) fluctuations in the elderly [6, 7].

In this background our study has been carried out to estimate seasonal variation of stroke and asses the role of various influencing modifiable factors like BP variation in a tropical region in influencing incidence of individual stroke types.

II. Methods

A prospective study was conducted upon 1440 cases of CVA admitted at Calcutta National Medical College, Kolkata at Calcutta National Medical College and Kolkata between January 2013 and December 2013. Season was divided as winter (December-February), summer (March-May), monsoon (June-August) and autumn (September-November). The time of onset of stroke was defined as the time when neurological symptoms first appeared. The subjects were categorized in to two major groups like ischemic and intracerebral hemorrhagic stroke based on non contrast brain CT scan and clinical features. Complete clinical history was noted with special attention to age, season, duration of complaints, family history and personal history like presence of hypertension, diabetes mellitus, tobacco smoking. Routine blood test including lipid profile was performed upon all the subjects.

Statistical analysis was done using Statistical Package for Social Science (SPSS-17).For comparing multiple groups Analysis of Variance (ANOVA) was applied and for comparing two groups t-test was applied. The critical level of significance was considered at 0.05 level ($p<0.05$).

III. Results

A total of 1437 subjects admitted throughout the year were included of which 60.1% were males and 39.9% were females. The cases were categorized into 4 major groups based on the number of candidates admitted in each season (TABLE 1). The cases were age and sex matched as far as possible (TABLE 2, 3).The total number of IS and ICH cases in different seasons along with relative percentages were calculated (TABLE 4) and expressed graphically (Fig1).There was an clear-cut increase in the incidence of ICH cases in winter compared to other seasons .The risk ratio and 95% confidence interval for the occurrence of ICH stroke in winter compared to summer, monsoon and autumn was found to be higher (TABLE 5).The difference in systolic and diastolic blood pressure in ICH cases in winter months compared to rest of the year were found to be significant. However lipid profile values were found to be almost similar (TABLE 6).

IV. Discussion

The present study demonstrated a clear seasonal variation in the occurrence of all stroke events in both sexes.

In winters, the overall incidence of stroke was higher among men and women than in rest of the seasons. This difference was mainly due to ICH, which the most common type of stroke admitted or registered by far. However, there was also a seasonal difference in the occurrence of ICH [8]. The total number of ICH cases was highest in winter season compared to other seasons. In fact, the estimates of risk ratios for occurrence of ICH were higher in winter compared to rest of the seasons. Our results are consistent with findings from other studies. In a population-based study from Japan, [9] found significant seasonality in the incidence of all strokes, ICH, and cerebral infarctions. In a community-based stroke register study from Italy, cerebral infarctions were more frequent during winter and primary ICH during autumn [10]. Some studies have obtained different results for ICH [11]. Most of the studies in this field have been performed in countries with cold or temperate climates, but in a study from Israel the average daily incidence of stroke was approximately twice as great on hot days as on relatively cold days. It suggests that exposure to extreme temperatures, whether cold or hot, may increase the risk of stroke [12].

Studies in the Finmonica areas of adult Finnish population, noted a significantly higher incidence of IS and ICH in winter than in summer [13]. In our study the IS case incidence was higher in winter than rest of the year but much less compared to ICH cases. The biological reasons for the higher occurrence of strokes during winter are not known, but several possible mechanisms may be suggested. Basic human physiology states that exposure to cold causes peripheral vasoconstriction and increase in blood pressure [14]. Moreover, total cholesterol and triglycerides levels tend to be higher in winter than in summer [15]. Most importantly, considerable seasonal variations, for plasma fibrinogen concentration and viscosity exist in elderly persons [16,17]. Other factors such as air pollution, exposure to sunlight, incidence of influenza, and diet have been also suggested to play a role, but variation in temperature has been considered the most likely reason [18].

Review conducted upon the seasonal occurrence of stroke in 2,960 patients at the University of Iowa from 1978 through 1985 showed that there was a significant increase in the rate of referral for IS during warmer months. Conversely, the rate of referral for ICH was significantly less during warm weather and rainy weather [19]. In our study however, statistically significant risk difference for occurrence of ICH was noted only between winter and summer seasons.

Other findings showed that the incidence of primary intracerebral haemorrhage was increased at low temperatures, but there was no significant relation between the incidence of ischaemic stroke or subarachnoid haemorrhage and temperature [20].

In our study except for SBP and DBP significant differences in serum lipid profile between winter and rest of the season was not observed among ICH cases.SBP and DBP showed significant univariate relationships with the season more than with temperatures [21]. The suggested aetiology was that cold increases sympathetic nervous activity, by elevating blood pressure and plasma and urinary catecholamine concentrations [22]. Muscle sympathetic nerve activity has been reported to have a role in BP regulation in humans. Cutaneous vasodilatation, loss of water and increased sodium excretion due to sweating cause lower BP in warm temperatures [23]. Opposite phenomena have been implicated as potential mechanisms for BP rise in cold conditions.

Vascular wall rigidity also influences BP. Arterial stiffness is related to winter-summer differences in SBP, but not with DBP. Similarly increased plasma Norepinephrine (NE), plasma renin activity (PRA), and plasma aldosterone (PA) are thought to participate in mediating hemodynamic changes from summer to winter [24].

Ninety-six men and women, age range 65-74 years, recruited from a single group general practice in Cambridge were found to have both systolic (SBP) and diastolic blood pressure (DBP) were greatest during the winter across the whole distribution of blood pressure. The increase in winter compared to summer was more evident in subjects with blood pressures > 160/90 mmHg. Older adults show more seasonal BP variation and this may explains partly the greater cardiovascular disease mortality of elderly subjects during the winter [25].

Similar cross-sectional survey carried out on a rural Ghanaian population, investigating the effect of ambient temperature on blood pressure in 574 adults aged between 18 and 65 years showed a significant inverse relationship between ambient temperature and systolic (SBP) and diastolic blood pressure (DBP). SBP fell by 5 mmHg per 10ºC rise in ambient temperature [26]. Influence of gender on modifying the relationship between temperature and BP varid from one study result to another [27,28]. Many studies report a seasonal pattern to stroke which has a strong relationship with BP [26].

In cold conditions, neurohumoral responses help increase heart function and maintain BP and organ perfusion. However chronic activation of these responses is detrimental causing imbalance between myocardial-stimulating and vasoconstricting hormones and between myocardial relaxing and vasodilating hormones [29].

Evidence shows that BP differs between geographical areas. Colder climates are associated with higher BP measurements. Similarly residents in regions with greater seasonal temperature differences show greater BP fluctuations [30].

Study conducted upon a large elderly population with hypertension living in a subtropical East Mediterranean region showed an 18% seasonal variation in BP [31]. Different racial and ethnic groups react differently to temperature changes. It suggests that temperature is a contributor to the higher cardiovascular mortality observed in African-Americans compared to Caucasians [32]. Animal model studies show that stroke-prone rats have exaggerated BP responses to cold exposure [27].

The limitation of the study includes consideration of cases admitted only in a tertiary care hospital whereas a large number of stroke patients are admitted in district and sub divisional hospitals. Potential confounding sources for rise in BP include lifestyle factors such as diet, diurnal variations but these are highly unlikely considering the cross-sectional nature of the study. Moreover multicentric study upon a larger population spanning over several years would have probably been helpful to increase the accuracy to determine relative risk ratio for ICH occurrence in winter compared to other seasons even further. None the less, stroke is the third largest cause of mortality in India after heart attack and cancer. Given the increasing incidence of ICH stroke during winter, encouraging physicians to widen the use of long acting antihypertensive drugs would contribute significantly to the primary prevention of ICH.

V. Figures And Tables

Table 1: Age and sex distribution of cases across four seasons

MEAN AGE (In Years) ± SD	WINTER	SUMMER	MONSOON	AUTUMN
FEMALE	62.35±12.93 (n= 272)	63.63±11.18 (n=104)	63.08±11.26 (n= 99)	63.03±11.59 (n= 98)
MALE	63.28±12.32 (n= 373)	62.33±10.01 (n= 147)	63.44±10.51 (n= 157)	61.44±9.66 (n= 187)
TOTAL (Season wise)	62.82±12.63 (n= 645)	62.98±10.59 (n= 251)	63.26±10.89 (n= 256)	62.24±10.63 (n= 285)
TOTAL(rest of theyear;summer-autumn)		62.83 ± 10.7 (n=792)		

n= Number of cases; SD=Standard Deviation

Table 2: Analysis of Variance (ANOVA) for mean age (In years)) ± standard deviation between cases in different seasons

	Sum of Squares	Difference	Mean Squares
Between Groups	142.22	3	47.41
Within Groups	193408.15	1436	134.69
Total	193550.37	1439	
F Statistic	0.3520		
p value	< 0.788		

* p value significant at < 0.05

Table 3: Chi-square test of Independence for number of CVA cases in each sex in various seasons

	WINTER	SUMMER	MONSOON	AUTUMN
MALE (n)	373	147	157	187
FEMALE (n)	272	104	99	98
Chi square	Difference	p value	Cases (n)	
5.5150	3	< 0.138 s	1437	

* p value significant at < 0.05; n: Number of cases

Table 4: Incidence of ICH and IS stroke cases in different seasons

	WINTER n, (%)	SUMMER n, (%)	MONSOON n, (%)	AUTUMN n, (%)	Total n, (%) Rest of the year
ICH	402(62.33)	138(54.99)	155(60.55)	180(63.16)	473(59.72)
IS	243(37.67)	113(45.01)	101(39.45)	105(36.84)	319(40.28)
Total	645	251	256	285	792

n: Number of cases; ICH: Intracerebral Haemorrhage; IS:Ischaemic Stroke

Table 5 Relative risks for occurrence of ICH stroke in winter compared to other seasons

ICH INCIDENCE	WINTER versus			
	SUMMER	MONSSON	AUTUMN	Rest of the year
Odds Ratio	1.3546	1.078	0.965	1.1157
95% CI	1.0083-1.82	0.801– 1.45	0.72 – 1.29	0.9 – 1.38
z statistics	2.015	0.496	0.242	1.006
p value	0.043	0.62	0.81	0.315

* p value significant at < 0.05; ICH: Intracerebral Haemorrhage; CI: Confidence Interval

Table 6: Comparison of blood pressure levels and serum lipid profile between ICH cases in winter and rest of the year

(Mean ± SD)	ICH (Winter)	ICH (Rest of the year)	p value
Systolic blood pressure	164±6 mm of Hg	154±10	< 0.0001
Diastolic blood pressure	100 ± 4 mm of Hg	94 ± 6	< 0.0001
Serum Cholesterol	201±61 mg%	204±63	0.065
Serum Triglyceride	180±60 mg%	175±40	0.06
Serum LDL-C	139±30 mg%	133±36	0.071
Serum HDL-C	35±10 mg%	36±19	0.227

* p value significant at < 0.05; SD=Standard Deviation; ICH: Intracerebral Haemorrhage
LDL-C=Low Density Lipoprotein Cholesterol; HDL-C= Density Lipoprotein Cholesterol; Hg=Mercury

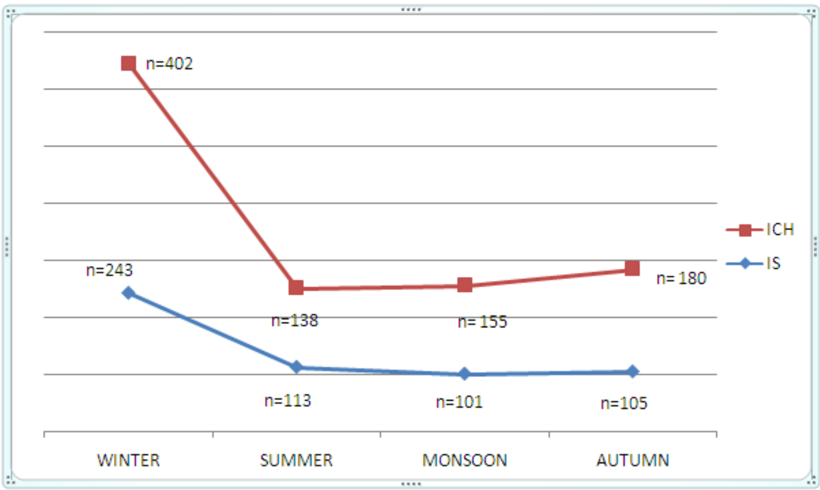

Fig 1 Line chart depicting incidence of ICH and IS cases in different seasons

ICH: Intracerebral Haemorrhage; IS:Ischaemic Stroke; n= Number of cases

VI. Conclusion

The results indicate the need for prospective multicenter studies with serial assessment of modifiable risk factors like BP, to assess the impact of these factors on prevalence and pathogenesis of ICH.

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