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Study of The Presence of Conventional And Newer Risk Factors in The Patients of Stroke and Its Relation With Outcome

KEYWORDS

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ABSTRACT *Background: Acute cerebrovascular accidents or commonly called as stroke have become the leading cause of morbidity and mortality in most of the nations of the world. The aim of the present study was to estimate the presence of existing(conventional)risk factors like hypertension, diabetes mellitus, dyslipidemia, tobacco use, obesity and emerging risk factors like hyperhomocysteinemia, raised CRP levels, raised ferritin levels, raised lipoprotein(A) levels and presence of hypercoagulable states.The present study also tried to find out any association with the presence of risk factors and the outcome of stroke in terms of neurological improvement.*

Methods and Results:A one point prospective study was conducted among a total of 75 patients who were railway employees aged 16 years and above (N=75), and had presented to the Emergency room or the neurology OPD with stroke of less than 30 days duration Evaluation for conventional cerebrovascular risk factors like body mass index, blood pressure, serum lipids, blood glucose levels and newer risk factors like serum hs-crp levels, serum lipoprotein (A levels),serum homocysteine levels, serum ferritin levels were performed using standard definitions. The mean age of the study population was 55.2 + 12.3 years. There was a high prevalence of major cerebrovascular risk factors like smoking in 16(21.3%), diabetes mellitus in 20(26.7%), hypertension in 63(84%), dyslipidemia in 63(84%),raised hs-crp levels in 32(69.3%),raised lipoprotein A levels in 42(56%),raised homocysteine levels in 67(89.3%),raised ferritin levels in14(18.67%) and presence of hypercoagulablestates in 34(45.33%).All the patients were evaluated for any improvement in the power of affected area of body at the time of admission to neurology unit and at the end of 3 months. Any relation to the presence of risk factors and course of outcome in terms of improvement in muscle power was studied.

Conclusion: The study demonstrated an overall high presence of the cerebrovascular risk factor more from the conventional ones and some from the newer ones in the railway employees affected with stroke but its association with the course of outcome was not present. This study gives us an insight to the risk factors among the railway employee population and also explains the need to initiate a comprehensive health promotion and cerebrovascular disease prevention programme at workplace and community level.

INTRODUCTION

All over the globe there has been a shift in the disease pattern from the infectious to the non-communicable diseases. Improvement in the education, nutrition and technology had led to early detection and better management of infectious diseases. On the contrary, due to

urbanization, industrialization and increased need for a better life has pushed the stress levels high and combined with a haywire lifestyle has lead to a surge in the development of non-communicable illness. As India has moved from being a developing nation to a developed nation, it is at present facing a double burden of both infectious and non-communicable diseases.

Of all the non-comminucable disease, the cardiovascular and the cerebrovascular accidents are the more commoner ones. Cerebrovascular accidents or more commonly known as strokes is one of the leading cause of mortality and morbidity worldwide. Approximately 20 million people each year will suffer from stroke and of these 5 million will not survive (Dalal et al 2007)(1,2). The Global Burden of Disease (GBD) Study (1997) reported 9.4 million deaths in India, of which 619, 000 were from 'Stroke,' and the Disability Adjusted Life Years (DALYs) that were lost, almost amounted to 28.5 million: nearly six times higher than that due to Malaria(3). In 2005, stroke deaths accounted for 87% of all deaths from developing countries and this burden will increase with ageing population(3). An estimated 5.7 million people died from stroke in 2005 and projected deaths will rise to 6.5 million by 2015(3).

Non-modifiable stroke risk factors include, age, sex, low birth weight, ethnicity and genetic factors, but modifiable risk factors include obesity, smoking, hypertension, high cholesterol and glycemic control in diabetics.

Risk factor plays a very important role in the development of any disease. It is one of the main tools used for the screening and prevention of the disease in the exposed population by means of risk factor modification.Risk factors can be either modifiable like environmental, acquired or non-modifiable like genetic. Few studies estimate the risk factors for stroke among the Indian populations, but, of the available data, the following figure 1 illustrates the prevalence of these risk factors, odds ratios and the population attributable risk proportion. As comparison, odds ratio of modifiable risk factors are also provided for the United States (US) population, for example; heart disease and smoking appear to be greater risk factors for the Indian compared with the US population.

Although stroke risk assessment tools exist, the complexities of the interaction between risk factors and the effects of certain risk factors stratified by age, gender, ethnicity and geography are incompletely captured by a global risk assessment tool.So evaluation of risk factors does give us

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an insight into the nature and progression of the disease and its possible prevention by risk factor modification.

Our attempt in this study has been to find out the presence of some modifiable risk factors like obesity, hypertension, diabetes mellitus, dyslipidemia, smoking and newer risk factors like elevated hs-CRP, raised lipoprotein A, raised ferritin, homocystenimia and the presence of any hypercoagulable states in the patients of CVA prospectively and to analyse if any correlation between the risk factors and the outcome exist.

METHODS

Study design and Setting: A prospective study among the railway workforce and their family members aged 16 years and above with recent onset stroke was conducted at Dr.BabasahebAmbedkar Memorial Hospital at Mumbai during the period from June 2013to June 2015.75 consecutive cases presenting with history of CVA of less than 30 days duration (recent onset stroke) and for the first time were included in the study group. All cases underwent a detailed history and clinical examination.

Biochemical investigations and imaging: The patients then underwent investigations like complete hemogram, Blood sugar---Fasting and Post prandial, Lipid profile (Tot.Cholesterol, Triglycerides, HDL & LDL),Serum Hs-CRP,Serum Lipoprotein A(LpA),Serum Homocysteine level, Serum Ferritin, Anti-phospolipid antibodies (IgM, IgG),Anti-cardiolipin antibodies (IgM, IgG), Serum Protein C activity,Serum Protein S activity, Anti-Thrombin III levels.

A provisional diagnosis was reached based on the history, examination and blood investigations.All the patients were then subjected to CT Brain plain or contrast as needed. Based on the CT brain , history, clinical examination, blood investigations and ECG a final diagnosis was reached.During the course of study it was decided that patients with normal CT findings would undergo an MRI Brain or MRA as needed for localisation of area affectedand for confirmation of diagnosis.

CVA was defined as sudden onset of neurodeficit due to a vascular cause and was sub typed as Infarct, TIA and IC Bleed as per the etiology.Treatment according to the type of CVA was given as per stroke guidelines in these cases. All patients were followed for the improvement in power of the affected group of muscles at the end of 3 months. An increase in one grade of power from the power at presentation of CVA was taken as improved case. Stastical analyses was done using Chi square test, one way ANOVA test and modified Kruskal-Wallis test.

Definitions:

RISK FACTOR:A "risk factor" is a condition or a behaviour that occurs more frequently in those who have or are at a greater risk of getting a disease than in those who don't. In our study we have considered the presence of conventional and newer risk factors in CVAs and their prognostic significance.

CONVENTIONAL RISK FACTORS(CRF):

Hypertension: According to American Heart Association and JNC 7 recommendations, hypertension is defined as systolic blood pressure(SBP) >= 140 mmHg with diastolic blood pressure (DBP) >= 90 mmHg or current use of anti-hypertensive drugs for maintaining a BP <140/90 mmHg. Blood pressure was measured in the right arm of the patient in supine position after a rest of 5 minutes to allay anxiety. An average of 2 consecutive BP readings were calculated. In this study we have taken SBP/DBP>=140/90mmHgor current use of anti-hypertensive drugs for maintaining a BP <140/90 mmHg as hypertension.

Diabetes Mellitus(DM): Diagnostic criteria laid down by American Diabetes Association in 2007 for diabetes mellitus are as follows-(any 1 of the 3 criteria)

- Symptoms of diabetes(polyuria, weight loss, polydypsia, polyphagia) with a random blood glucose concentration greater than or equal to 200 mg/dl
- Fasting blood glucose concentration >=126 mg/dl
- 2 hour post prandial plasma glucose >=200mg/dl

Presence of any one of the above three factors were considered as presence of DM and as risk factor for CVA in this study.

Dyslipidemia: Increased LDL, Increased TG, Decreased HDL and Increased Cholesterol levels will finally give rise to increased atherogenecity. Dyslipidemia is said to be present when;

- HDL <40mg/dl (Men) or HDL<50mg/dl (Women),
- LDL > 100mg/dl,
- Total cholesterol >200mg/dl and
- TGA>150mg/dl.

The presence of any one or more of the above factors was considered as presence of dyslipidemia.

Tobacco Smoking: Smoking tobacco increases the risk of developing vascular diseases like cerebrovascular accidents, coronary artery disease, peripheral vascular disease etc(45). It increases atherogenecity, increases hypercoagulable states.

Smokers were classified as current smokers and ex-smokers (who have quit smoking 1 month back).

	Obesity Class	BMI(kg/m2)
Underweight		<18.5
Normal		18.5-22.9
Overweight		23-27.9
Obesity	I	28-32.9
	II	33-37.9
Extreme obesity	III	>=38

Obesity:

Probable mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system and altered vascular function. Adiposity promotes cardiovascular risk clustering(83). Classification of overweight and obesity was done according to the Body mass index (BMI) is shown below.(Harrisons Text of Medicine 18thed.)In this study BMI>=28 was taken as obesity and as a significant risk factor for CVA.

NEWER RISK FACTORS(NRF):

Hs-CRP: It is an acute phase reactant of pentraxin family produced by hepatocytes induced by the release of interleukin-1 and interleukin-6 that reflects activation of system-

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ic inflammation. It is a significant independent risk factor for stroke, coronary heart disease and for development of hypertension(52). American Heart Association and US-CDC defines hs-CRP with risk of CAD/CVA/PVD as :

- Low risk - <0.1mg/dl
- Average risk 0.1 to 0.3 mg/dl
- High risk >0.3 mg/dl.

Presence ofhs-CRP levels >0.3mg/dl was considered as high risk for CVA in our study.

Lipoprotein-a [Lp (A)]: Lp(A) is a plasma lipoprotein which was identified in1963 by Kare Berg and exhibits high structural similarity with low density lipoprotein (LDL) cholesterol(16). It consists of LDL like particle and specific apolipoprotein 'a' covalently bond to the apo B of the LDL like particle. It competes with plasminogen for its binding site leading to decreased fibrinolysis, also stimulates Platelet Activating Factor-1 leading to thrombogenesis. There is an evidence that Lp(A) is a predictor of many forms of vascular disease, including premature coronary, peripheral and cerebral artery disease(51,52).Normal Lp (A) <14mg/dl in serum.High risk of thrombogenesis is present when the levels are >30mg/dl.We have consideredLp(A) levels more than 30mg/dl as a risk factor for CVA in our study.

Hyperhomocysteinemia: Acts as a thrombophillic agent causing increased atherogenesity. Normal Serum homocysteine<12 mmol/ml. Levels more than 12 mmol/ml increases the atherogenic risk of an individual. Levels more than 12mmol/ml were considered as risk factor for CVA.

Serum Ferritin: Sullivan's Iron hypothesis (1981) says raised iron stores(ferritin) causes oxidative imbalance(2,3). In Fenton's reaction Fe(II) catalyses the formation of extremely reactive hydroxyl radicals. Interaction with the lipids may initiate the formation of oxidised LDL that ultimately lead to formation of foam cells and progression of atherosclerosis. Ferritin also plays a vital role in vascular disease by activation of platelets by protein kinase C mechanism.Serum ferritin level >300ng/ml (males) and > 200ng/ml (females) was considered as a risk factor for CVA.

Hypercoagulable states: It is characterised by decreased protein C, decreased protein S, decreased antithrombin III levels and increased levels of ACLA and APLA antibodies.

Protein C – It is a Vit K dependant protease principally produced in liver acts as an anticoagulant, inactivates Factor Va and VII a and enhances fibrinolytic activity in plasma.Normal range of protein C activity is 70 – 140%.Less than 70% activity increases the risk of thrombogenesis. In our study less than 70% activity was considered as significant for hypercoagulable states.

Protein S –It is produced in liver and acts as a co-factor for protein C. Reduced protein S is responsible for venous thrombosis more rather than arterial thrombosis. Normal range of protein S activity is 70-140%.Less than 70% activity increases the risk of thrombogenesis. In our study levels less than 70% was taken as significant for hypercoagulable states.

Antithrombin III –It is synthesized in liver and circulates in the plasma. It inactivates thrombin, plasmin, factor IXa, Xa, XIa and XIIa. Decreased activity will increase the atherogenesity. Normal activity is 70-130%. Less than 70% activity increases the risk of thrombogenesis and was taken as risk factor of CVA in our study.

APLA& ACLA: Antiphospholipid antibodies consist of several related, but somewhat clinically distinct subgroups, including lupus anticoagulants (LA), anticardiolipin antibodies (ACLAs), and a number of less well characterized and investigated antiphospholipid antibodies(66,67).ACLAs and LA occur in approximately 5% and 4%, respectively, of the general population. Antiphospholipid antibodies have been associated with venous thromboembolism as well as arterial thrombosis, including coronary thrombosis, stroke, and transient ischemic attacks.The APLA is frequently found in sera of SLE patients and related disorders. There is a correlation between these 2 auto antibodies and the enhanced incidence of thrombosis,atherogenosis, thrombocytopenia and habitual abortion. Normal levels of APLA-IgG<15 U/ml, APLA-IgM<15 U/ml.Normal values of ACLA-IgG<15U and ACLA-IgM<15U. Levels greater than 15U/ml increases the risk of thrombogesis. We have considered values >15U/ml of APLA-IgG and IgM as significant for hypercoagulable states.

RESULTS

Of the 75 cases of CVA included in this study 5 patients (6.67%) belonged to age less than 40 years, 52 patients (69.33%) were in the age between 41 to 60 years and 18 patients (24%) were above 60 years.

Among them the minimum age was 18 years and maximum was 82 years. The mean age was 55.16 years with a standard deviation of 12.23 years.

Out of the total study population 72% were males and 28% were females indicating that higher rate of CVA in men in this study.Infarcts were the commonest type of CVAs seen (70.66%) followed by intra cranial bleeds (16.00%). 13.34% of the total CVAs were transient ischaemic attacks.

54 cases(72.00%) were males of which 41 patients had infarcts (75.92%), 8 patients had intra-cranial bleed (14.81%) and 5 cases with TIA (9.25%). Also there were 21 female patients which consisted 28% of the total patients of which 12 patients were having infarcts (57.14%), 4 patients had intra-cranial bleed (33.33%) and 5 cases had TIA (41.67%).

Only 4 patients were obese (5.33%) of which 3 were females (75.00%) and 1 patient was male(25.00%). Amongst the obese individuals 1 patient had infarct (25.00%) , 1 patient had bleed(25.00%) and remaining 2 cases had TIA ((50.00%).16 patients(21.33%) were smokers of which all the 16 patients were males (100%). 68.75% of the total smokers had infarcts, 18.75% smokers had IC-bleed and 12.50% smokers had TIAs.

There were 84% patients who had hypertension and had a CVA. Amongst the hypertensive population, it was seen that 65.07% had infarcts, 19.04% had IC-bleeds and 15.87% had TIAs. All the patients with IC-bleed and TIA were hypertensive(100%).

There were 20 patients(26.67%) out of 75 patients who had diabetes mellitus and stroke. Out of these 20 patients it was seen that 70% patients had infarcts, 20% patients had IC-bleed and 10% patients had TIA.The incidence of dyslipidemiawas 68.25% patients who developed infarcts, 17.46% patients who developed IC-bleed and 14.28% patients had TIA. But a higher percent of non-dyslipidemic population developed infarct(83.33%).Females formed

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greater part of dyslipidemics who had a stroke (85.71%). There were 67 patients who had raised serum homocysteine levels(89.33%). Among them there were 71.64% patients who had infarct, 14.92% patients had IC-bleed and 13.43% patients had TIA.Only 14 patients who had raised serum ferritin levels with CVA. Of these 64.28% patients had infarct and 35.71% patients had IC-bleed.45.33% with stroke had presence of hypercoagulable state. Amongst these patients there were 79.41% patients had infarct, 8.82% patients had IC-bleed and 11.76% patients had TIA.

From the table 1, it is seen that presence of hypertension(84.00%), dyslipidemia(84.00%), raised serum homocysteine level(89.33%) seemed to increase the risk of developing a stroke. When compared individually each of these risk factors present and absent in those who developed stroke, there seems to be no significant relation between the presence of most of above mentioned risk factor and development of stroke($p>0.05$). But hypertension seems to have a direct and independent relation with the development of CVA($p=0.037$) especially in the IC bleed and TIA patients, all of which were hypertensives.

All the patients were followed at the end of 3 months for assessment of their neurological status. Any improvement in the power of the affected group of muscles, GCS, reversal of palsy or any improvement in the MMSE were considered as the *Improved* (neurological status improved) group. No change in the neurological status at the end of 3 months were considered as the *Same* (neurological status same) group. All the patients who expired in these 3 months were considered in the *Expired* group.

69.33 percent cases showed some type of improvement in their neurological status, 22.67 percent cases remained neurologically same and 8 percent cases (n=6) expired before the follow up and66.67 percent of males and 76.19 percent of females improved prior to the follow up. There were 27.78 percent of males and 9.52 percent of females whose neurological status remained the same at the time of follow up. 5.56 percent of males and 14.28 percent of the females died prior to the follow up.Of the 52 improved cases 67.30 percent were infarcts, 13.46 percent were bleeds and 19.23 percent had a TIA. All the TIAs which occurred improved. There were 17 cases who had the same neurological status at the time of follow up of which 94.11 percent were infarcts and 5.88 percent were bleeds. Of the 6 cases who died prior to the follow up, 66.67 percent were bleeds and 33.33 percent were infarcts indicating that bleeds had a higher chance of death as compared to the infarcts. All the IC- bleeds expired within first week of having the stroke and were hospital deaths.

Each risk factor was considered as a single variable and were counted for each class of the outcome for determining the relationship between the presence of number of risk factors and the outcome. The risk factors were divided into 2 separate groups of conventional risk factors (CRF) and non-conventional risk factors (NRF).Of the total 75 cases, 49.33 percent of the patients had 2 CRF followed by 26.67 percent cases who had 3 CRF, then 14.67 percent cases who had 1 CRF. 4 patients did not have any CRF still they had a CVA(5.33%). Only 3 patients had maximum of 4 CRF(4.00%).Out of 4patients who did not have any CRF, all of them improved neurologically(100%). Among the patients having maximum CRF of 4, 66.67 percent improved and33.33 percent did not show any neurological improvement. Among the 11 patients who had only one CRF, 45.45% remained neurologically same, 36.36 percent improved neurologically and 2 patients expired(18.18%). 49.33 percent of the study population had 2 CRF, of which 70.27 percent improved, 21.2 percent had no neurological improvement and 3 patients expired(8.10%).Out of the 20 patients (26.67%) who had 3 CRF, 80 percent improved neurologically, 15 percent remained neurologically same and 1 patient expired(5.00%). Among those who died prior to follow up 50 percent had two CRF, 33.33% had one CRF and 1 patient had three CRF (16.67%).

Among the total study population there were 2 patients who had the presence of all the five NRF(2.67%) and they did not show any improvement in their neurological status(100%).

40 percent of the cases had 3 NRF of which 21 patients(70.00%) improved, 16.7 percent remained neurologically same and 4 patients expired(13.33%).29.33 percent cases had 2 NRF of which 14 patients improved(63.63%), 31.81 percent remained neurologically same and 1 patient expired(4.54%). 16 patients had 4 NRF of which 12 patients improved (75.00%) followed by 4 patients who had 1 NRF of which all improved (100%).

There was only one patient who did not have any NRF and his neurological status showed improvement at the time of follow up(100%).Except for the type of CVA rest all other risk factors considered in this study failed to show any significance with the outcomes (p value>0.05).Among the different CVAs, IC-bleeds seem to have a bad prognosis as far the mortality was concerned ($p=0.001$). One way Anova test was used to study the significance of the age on the prognosis but it did not show any significance in this study. For the relationship between the number of risk factors and the outcome of stroke mode of risk factors was used and the results were subjected to Kruskal- Wallis test (table 5). From the analysis we found that there doesnot exist any correlation between the number of the risk factors and theoutcome of the stroke ($p>0.05$).

DISCUSSION:

A total of 75 patients were included in this study of presence of conventional and newer risk factors in the stroke patients and their prognostic significance. Of the 75 cases of stroke 54(72%) were males and 21(28%) were females. Males seem to have higher incidence of strokes as compared to the females. This seems to hold true as Peter Appelros et al had showed that male stroke incidence rate was 33% higher than the female, with large variations between age bands and between populations (4,5). Also our study had 41 males(77.4%) and 12 females(22.6%) with cerebral infarction and 8 males(66.7%) and 4 females(33.3%) with intracerebralhemorrhages. The remaining 10 patients who had TIAs had 50% of males and females each.This has also been shown in the metanalysis study by Peter Appelros et al (4) and Roquer J (5) that incidence rates of brain infarction and intracerebralhemorrhage were higher among men, although this difference was not statistically significant. Stroke seemed to be more severe in women, with a 1-month case fatality of 24.7% compared with 19.7% for men (4,5,6). In our study age did not play any role in predicting the poor prognosis of stroke($p=0.794$).

Obesity can increase the risk of stroke by having excessive fat tissue throughout the bodywhich leads to an increased risk of atherosclerosis(7,8,9,10). Among the conventional risk factors taken in our study the obesity had been pre-

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sent only in 4(5.3%) patients, hence obesity per se did not play a significant role in this study. Contrary to the study done by Amytis T where in the prevalence of obesity was 47.4% in the stroke population.

Hypertension affects at least 65 million persons in the United States and is a major risk factor for both cerebral infarction and intracerebralhemorrhage (Fields *et al.*, 2004)(11). The higher the blood pressure, the greater the stroke risk (Lewington*et al.*, 2002)(12). Chobanian*et al* (2003) reported that control of high blood pressure contributes to the prevention of stroke as well as to the prevention or reduction of other target organ damage, including congestive heart failure and renal failure(13). Risk of stroke can be reduced by at least 38% by control of hypertension (MacMahon and Rodgers, 1996) (14).

According to the NHANES study 37.43% of the stroke patients had hypertension (p=0.03) which shows a causal relationship (15). Similarly in our study we had 63 patients (84%) who had hypertension. Hypertension seemed to have a greater impact on the intra cerebral bleed and the TIA subgroup which had all cases with hypertension (100%). Khan et al has shown hypertension as a predominant risk factor in his study of 91 stroke cases which had 56.04%(51 patients)of its patients with hypertension (16). In Chinese and Australian studies risk of stroke was higher in hypertensive patients as compared to normotensive patients (17,18).

In comparison with Khan et al our study had a higher number of hypertensives suffering from stroke(n=84%). But our study did not show any significance in having raised blood pressures in stroke associated with poor neurological outcomes(p=0.218).Wolf described the prediction of stroke based on the Framinghamcohort study(19). During a 10-year follow up in the Framingham Study comprising individuals age 55-84 years, there were 472 strokeevents among 2,372 men and 3,362 women. Approximately11% of men and 8% of women had diabetes. The risk of stroke was adversely related to the presence of diabetes in both men (relative risk 1.40) and women (relative risk 1.70)(19).

Similarly, the Copenhagen City Heart Study evaluated 3,015 men and 3,501 women age 55-84 years. There were 474 strokes over a 10-year period. Only 3% of men and 2% of women had a history of diabetes(20). The 30-year followup of the Framingham Study found that blood glucose level was an independent risk factor for stroke and the risk of stroke was increased for both diabetic men and women(21).McCall has noted that a higher blood glucose level at hospital admission predicts a poorer prognosis after a stroke, irrespective of whether the patient is diabetic or not. Also, the degree of disability after the stroke may be worse among individuals with elevated blood glucose at the time of the stroke(22). In our study we found that 26.67% (20 patients) patients were diabetics of which 70 percent had infarcts. Of these 2 patients expired(10%) and 15 patients(75%) improved in their neurological status.

Contrary to McCall our study did not show increased level of poor outcomes in diabetics(p=0.616), but in accordance with the Framingham and Copenhagen studies our study did show a significant percentage of diabetics suffering from stroke(26.7%).Dyslipidemia being the most common cause of atherosclerosis, leads to a majority of vascular disease of which stroke is one. Studies by Zhang et al and Khan et al have shown that dyslipedimia as a modifiable risk factor was present in the stroke population (23,24).

From our study we found out that of the 75 patients of stroke, 63 patients were dyslipidemic (84.00%). Among these 43 patients accounted for infarction (68.25%) and 11 patients for bleed (17.46%) and 9 patients for TIAs (14.28%).Hence dyslipidemia was present in maximum of the ischemic events (82.53%).

Tjiomalos et al have shown that raised LDL cholesterol was an independent risk factor for stroke among the dyslipidemic population (25). Similarly out of 63 dyslipidemic patients in our study we had 37 patients with raised LDL cholesterol (49.30%).Also we noticed that of these 63 patients there were 35 patients who had decreased HDL cholesterol (46.70%). From this we can say that along with raised LDL cholesterol, reduced HDL cholesterol is also an independent risk factor in the development of stroke. Our study did show 19 patients with raised serum cholesterol (25.30%) and 13 patients with raised serum triglycerides (17.30%) but increased LDL -c and reduced HDL-c were more prevalent. Of the 63 dyslipidemics 43 patients improved at the end of 3 months, 14 patients remained neurologically same and 6 patients expired. We did not find any significance of dyslipidemia in relation to the outcome of stroke but those patients who expired were all dyslipidemics(p=0.499).

Over the past few decades cigarette smoking has been established as a major risk factor for the development of cerebral infarction (26,27,28,29). In a meta-analysis of 22 studies of the association between cigarette smoking and stroke prior to 1988, Shinton and Beevers found that the relative risk for cerebral infarction associated with smoking was 1.92 (95% CI, 1.71-2.16) (30).Similar results have been obtained in cohort studies in the United States and Taiwan (31,53,54,55). In the U.S. Physicians' Health Study, Kurth and colleagues found that current smoking was associated with a twofold increase in the risk of ischaemic stroke (RR 2.11, 95% CI, 1.72-2.60) (31). In our study of 75 patients, we had only 16 smokers who had stroke(21.33%).Among the 16 smokers 11 patients developed infarction(68.75%), 3 patients developed IC bleed(18.75%) and 2 patients had TIA(12.50%).

Hence our study did not show an increased prevalence of smokers developing stroke as compared with the above mentioned studies but it did show an increased percentage of smokers developing cerebral infarction rather than TIA or hemorrhage. Also we did not find any significant relation between smoking and poor outcome of stroke as only 5 smokers failed to have any neurological improvement at the end of 3 months(p=0.318).Inflammation plays a critical role in the development of vascular disease, and increased levels of the inflammatory biomarkers, lipoprotein- A (Lp-A), and high-sensitivity C-reactive protein (hs-CRP) have been shown to be associated with an increased risk for ischemic stroke(31,32). Our study showed that out of 75 patients there were 52 patients who had raised hs-CRP levels(69.33%).

Vijay et al showed raised hs-CRP levels to be associated with increased incidence of ischaemic stroke in his study of 949 patients(32). In our study of the 52 patients with raised hs-CRP levels 37 patients were infarcts(71.15%). Thus, presence of raised hs-CRP levels increases the incidence of ischaemic stroke and it contributes as an independent risk factor for stroke. But raised hs-CRP levels in our study did not have any significant relation with poor neurological outcome at end of 3 months (p=0.218).

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Lipoprotein(A) is an acute phase reactant and there is evidence that its raised levels are related to stroke(33,34,35,36).Barbara et al in her meta-anlysis have shown that elevatedLp(a) levels is a risk factor for incident stroke(37). Even the ARIC study suggested that Lp(a) levels are raised in stroke and they have a causative role in both blacks and whites(38). In our study 42 patients out of 75 patients had raised Lp(a) levels(56%).Hence our study did show a causal relationship between raised lipoprotein(A) levels and development of stroke. Of these 42 patients, only 3 patients expired which showed that the raised levels of Lp(a) did not have any significance with the poor outcome of stroke(p=0.899).

We also studied the presence of raised ferritin levels and stroke. Out of 75 patients there were only 14 patients who had raised ferritin levels(18.67%).Therefore we did not find ferritin to be an independent risk factor of stroke. High serum ferritin levels within the first 24 hours of hospitalization for an acute ischemic stroke are related to a poor prognosis, independent of the stress response(39). Ozbakir in his study showed that raised ferritin in stroke had poor prognosis but in our study ferritin did not have any significance in determining poor outcome of stroke (p=0.060) (40).

Epidemiological studies have linked elevated plasma total homocysteine concentrations with an increased risk of ischaemic stroke because of arterial disease(41,42,43,44). There are adverse effects of total homocysteine on vascular smooth muscle as it leads to cytotoxic and thrombophilic effects on vascular endothelium(41). Perry and colleagues in his study has shown that there was a strong independent correlation between raised serum homocysteine levels and the development of stroke(45). We found in our study that out of 75 patients we had 67 patients with raised homocysteinelevels(89.33%).

Of these 57 had ischeamicstroke(Infarction + TIA). Hence, our study showed a causal relationship between raised homocysteine levels and the development of stroke. As among these 67 patients only 5 patients expired, therefore we were not able to find any significance between raised homocysteine levels and poor outcome of stroke(p=0.857). The presence of antiphospholipid antibodies is considered a risk factor for stroke by some authors, however, some studies have shown no such association(46). The role of protein C and protein S deficiency in arterial thrombotic disease and stroke is also less clear. There are, however, several studies that have demonstrated the presence of protein C deficiency in stroke, either alone or in combination with other causes of a hypercoagulablestate (47,48,49,50).

Hence we considered the presence of the variables , decreased protein S or decreased protein C or reduced anti-thrombin III or presence of ACLA or APLA antibodies either in single or in combination to be a marker of hypercoagulable state in stroke patients of our study. By this consideration we found out that out of 75 stroke patients 34 patients had an underlying hypercoagulable state(45.33%).Even though we have used a crude method of considering a wide test spectrum for hypercoagulable state its presence in our stroke patients indicates it to be a significant risk factor. The presence of hypercoagulablestate on contrary did not have any significant relation in determining worse outcomes(p=0.811).We also calculated the presence of total number of conventional and newer risk factors among our study population(Table 21).Of the total 75 cases 49.33 percent of the patients had 2 CRF followed by 26.67 percent cases who had 3 CRF, then 14.67 percent cases who had 1 CRF.4 patients did not have any CRF still they had a CVA. 3 patients had maximum of 4 CRF and their neurological status did not show any improvement at follow up.

It was also noticed that of the total study population 52 cases showed some neurological improvement at the time of follow up of which 7.69 percent each had no CRF and a single CRF, 50 percent cases had presence of two CRF. Of the remaining improved cases 30.76 percent cases had three CRF and 2 patients had 4 CRF (3.84%). Of the patients with no CRF, all of them improved, 80 percent of patients with 3 CRF improved followed by 70.27 percent of patients with 2 CRF who showed improvement neurologically.Out of the 17 cases which didn't show any neurological improvement there were 29.41 percent cases who had presence of one CRF, 47.05 percent cases had two CRF, 17.64 percent cases had three CRF and one patient had 4 CRF(5.88%). Among those who died prior to follow up 50 percent had two CRF, 33.33% had one CRF and 1 patient had three CRF (16.67%). From table 21 we see that, of the patients with maximum CRF (n=4), 66.67percent patients improved and 33.33 percent of patients remained same neurologically at follow up.

From table 4, we can see that there were 2 patients who had the presence of all the five NRF(2.67%) and they did not show any improvement in their neurological status(100%).40 percent of the cases had 3 NRF of which 21 patients(70%) improved, 16.67 percent remained neurologically same and 13.33 percent patients expired. followed by 29.33 percent cases had 2 NRF of which 14 patients improved(63.64%). 16 patients had 4 NRF of which 12 patients improved(75%) followed by 4 patients who had 1 NRF of which all improved(100%). There was one patient who did not have any NRF and his neurological status showed improvement at the time of follow up. Kruskal –Wallis test was applied to findings of tables 3,4 and it showed that there was no correlation between the number of risk factors and the outcome [CRF:p=0.595, NRF:p=0.912](Table 5).Thus, in our study we did not find any significance between the number of risk factors and worsening stroke outcomes.

CONCLUSIONS:

Cerebral infarction was the predominant type of stroke(70.67%) in this study followed by intra cerebral bleed(16%) the transient ischaemic attacks(13.33%).Males were more affected by strokes than their female counterparts (72%vs28%).The type of stroke was the main factor which determined the neurological outcomes with bleeds having the worst and infarctions having better prognosis(p=0.001).Hypertension is a very important and an independent risk factor for stroke (p=0.037).But it did not have any significant role in determining the prognosis of stroke(p=0.218).

Diabetes mellitus increases the chances of getting stroke both as an independent risk factor and in combination with hypertension increases the incidence further(n=26.7%). There was no relation with diabetes and poor stroke outcomes(p=0.616).Dyslipidemia formed a greater part of the stroke modifiable risk factor accounting to 82.7% of study population.Raised LDL cholesterol and reduced HDL cholesterol was more common among the dyslipidemic population with stroke(49.3% & 46.7%).Dyslipidemia as a risk factor didnot have any relation with the neurological outcomes(p=0.499).Smoking was prevalent in 21.3% of

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study population and all the smokers were men. 68.75% of smokers had cerebral infarction. Smoking did not determine any relation with poor outcome of stroke(p=0.318). Only 5.3% of the study population was obese. Obesity was neither a contributory risk factor nor had any prognostic value for stroke in this study(p=0.393).Elevated hs-CRP levels were present in significant number of study population. It is an independent risk factor for stroke especially in the developmentof TIA (p=0.011).Elevated levels do not determine the neurological outcome(p=0.218).

Lipoprotein (A) levels are higher in stroke and it is an emerging new risk factor in stroke(56%). Elevated Lp(A) levels were found to be more in infarcts(66.67%).Raised levels does not have any significance in determining the neurological outcome (p=0.899).Hyper-homocysteinemia is a predominant newer modifiable risk factor for stroke due to ischaemia(71.64%) but it does not have any prognostic significance(p=0.857).Raised serum ferritin levels did not contribute to the development of stroke and doesnot have any role in predicting prognosis (p=0.060).Hypercoagulable states are present in strokes(45.33%). They donot have any prognostic significance(p=0.811).Neurological outcome or prognosis is independent of the presence of conventional or newer risk factors. [CRF:p=0.595, NRF:p=0.912] but it depends only on the type of stroke(p=0.001).

FIGURES

Figure 1:

Risk factors of stroke among the Indian population

	Prevalence of risk factors, India	Odds Ratio, India			Odds Ratio, US	PARP India
Study	Tripathi All ages	Bhattacharya All ages	Lipsaka All ages	Zodpey All ages	AHA All ages	Zodpey All ages
Alcohol consumption	22.5% #			1.96	1.8	0.09
Diabetes	3% - 12%	1.73		2.39	1.8	
Family history of stroke	8% *					
Heart disease	7% with AF ^	6.20		3.4	1.73	
High cholesterol	7% - 32%		0.2 per SD increment	2.27	2.0	0.14
Hypertension	12% - 40%	2.79	1.9 per SD increment	1.99	1.0 – 4.0	0.17
Obesity	6% - 49%			1.91	1.75-2.37	
Past history of TIA				8.44		0.08
Smoking	13%women 46% men	3.92	7.8	1.11	1.9	

PARP= population attributable risk population; AF=atrial fibrillation, ^ Sridharan et al 2009;
Bhattacharya 2005; # Shah 2005

Figure 2: Prevalence of risk factors in CVAs.

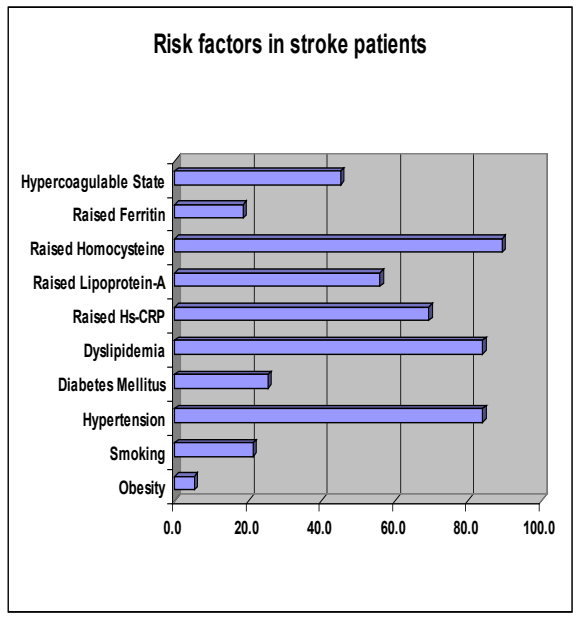

***Table 1: Demographic profile and Risk factors (Conventional / Newer)* profile of Stroke patients**

		Infarction	Bleed	TIA	Total
N		53	12	10	75
Age		54.8 ± 12.7 (18-82)	52.8 ± 7.9 (36-63)	60.2 ± 13.4 (39-80)	55.2 ± 12.3 (18-82)
Sex	Male	41 (77.4%)	8 (66.7%)	5 (50.0%)	54 (72.0%)
	Female	12 (22.6%)	4 (33.3%)	5 (50.0%)	21 (28.0%)
Conventional RF	Obesity	1 (1.9%)	1 (8.3%)	2 (20.0%)	4 (5.3%)
	HT	41 (77.4%)	12 (100.0%)	10 (100.0%)	63 (84.0%)
	DM	14 (26.4%)	4 (33.3%)	2 (20.0%)	20 (26.7%)
	Dyslipidemia	43 (81.1%)	11 (91.67%)	9 (90.0%)	63 (84.0%)
	Smoking	11 (20.8%)	3 (25.0%)	2 (20.0%)	16 (21.3%)
Newer RF	HS-CRP	37 (69.8%)	8 (66.7%)	7 (70.0%)	52 (69.3%)
	Lipoprotein a	28 (52.8%)	8 (66.7%)	6 (60.0%)	42 (56.0%)
	Hyperhomocystinemia	48 (90.6%)	10 (83.3%)	9 (90.0%)	67 (89.3%)
	Raised ferritin	9 (17.0%)	5 (41.67%)	0 (0.00%)	14 (18.67%)
	Hypercoagulable states	27 (50.94%)	3 (25.0%)	4 (40.0%)	34 (45.33%)

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Table 2: Comparison of Demographic profile and Risk factors (Conventional/ New)profile of CVAs with outcome (Prognosis)

		Improved	Same	Expired	P value	Significance
N		52	17	6		
Age		54.6 ± 11.9 (18-80)	56.9 ± 14.2 (20-82)	55.0 ± 10.2 (41-70)	0.794*	Not significant
Sex	Male	36 (69.2%)	15 (88.20%)	3 (50.0%)	0.145	Not significant
	Female	16 (30.8%)	2 (11.8%)	3 (50.0%)		
Diagnosis	Infarction	35 (67.3%)	16 (94.1%)	2 (33.3%)	0.001	Significant
	Bleed	7 (13.5%)	1 (5.9%)	4 (66.7%)		
	TIA	10 (19.2%)	0(0.00%)	0(0.00%)		
Conventionall RF	Obesity	4 (7.7%)	0(0.00%)	0(0.00%)	0.393	Not significant
	HT	46 (88.5%)	12 (70.6%)	5 (83.3%)	0.218	Not significant
	DM	15 (28.8%)	3 (17.6%)	2 (33.3%)	0.616	Not significant
	Dyslipidemia	43 (82.7%)	14 (82.4%)	6 (100.0%)	0.499	Not significant
	Smoking	11 (21.2%)	5 (29.4%)	0(0.00%)	0.318	Not significant
Newer RF	HS-CRP	34 (65.4%)	12 (70.6%)	6 (100%)	0.218	Not significant
	Lipoprotein a	30 (57.7%)	9 (52.9%)	3 (50.0%)	0.899	Not significant
	Hyperhomocystinemia	47 (90.4%)	15 (88.2%)	5 (83.3%)	0.857	Not significant
	Raised ferritin	7 (13.5%)	7 (41.17%)	0(0.00%)	0.060	Not significant
	Hypercoagulable states	22 (42.3%)	9 (52.9%)	3 (50.0%)	0.811	Not significant

(Chi-square test / * One way ANOVA test)

Table 3: Relationship of CRF and outcome of CVAs.

No.of CRF/ Outcome	Improved n=52	Same n=17	Expired n=6	Total N=75
0 CRF	04 (100.00%)	00 (0.00%)	00 (0.00%)	04 (5.33%)
1 CRF	04 (36.36%)	05 (45.45%)	02 (18.18%)	11 (14.67%)
2 CRF	26 (70.27%)	08 (21.62%)	03 (08.10%)	37 (49.33%)
3 CRF	16 (80.00%)	03 (15.00%)	01 (05.00%)	20 (26.67%)
4 CRF	02 (66.67%)	01 (33.33%)	00 (0.00%)	03 (4.00%)
5 CRF	00 (0.00%)	00 (0.00%)	00 (0.00%)	00 (0.00%)

CRF—Conventional Risk Factor

Table 4: Relationship between NRF and CVAs.

No.of NRF/ Outcome	Improved n=52	Same n=17	Expired n=6	Total N=75
0 NRF	01 (100.00%)	00 (0.00%)	00 (0.00%)	01 (1.33%)
1 NRF	04 (100.00%)	00 (00.00%)	00 (00.00%)	04 (5.33%)
2 NRF	14 (63.64%)	07 (31.81%)	01 (04.54%)	22 (29.33%)
3 NRF	21 (70.00%)	05 (16.67%)	04 (13.33%)	30 (40.00%)
4 NRF	12 (75.00%)	03 (18.75%)	01 (06.25%)	16 (21.33%)
5 NRF	00 (0.00%)	02 (100.00%)	00 (0.00%)	02 (2.67%)

NRF- Newer Risk Factor

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Table 5: Comparision of Conventional and Newer risk factor with the outcome.(Kruskal-Wallis Test)

	Improved	Same	Expired	P value	Significance
Conventional RF	3 (0-5)	3 (0-4)	3 (2-4)	0.595	Not significant
Newer RF	3 (0-5)	3 (0-5)	2 (2-4)	0.912	Not significant

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