HOMOCYSTEINE – RISK FACTOR FOR ISCHEMIC STROKE ?

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Abstract : The present study was undertaken to compare the homocysteine levels in patients of ischemic stroke with controls. Our study included 117 patients of ischemic stroke and 101 controls. The mean homocysteine levels in patients with ischemic stroke were 16.80 ± 6.71 umol/L while in controls it was 12.30 ± 4.68 umol/L, the difference being statistically significant ($P < 0.01$). The increased homocysteine levels in patients with ischemic stroke are independent of diabetes mellitus, age and sex. The homocysteine levels were higher in hypertensive subjects than non-hypertensive ($P < 0.05$).

Key words : ischemic stroke   homocysteine

INTRODUCTION

Stroke is a worldwide health problem. It is a major cause of morbidity, mortality and disability in developed as well as developing countries. The term stroke is applied to acute manifestations of cerebrovascular disease (1). After coronary heart disease and all cancers, stroke is the third common cause of death in the world, causing about 4 million deaths in 1990, and three quarters of them in developing countries (2). In India, neuroepidmiological data on stroke collected over the past thirty years have revealed prevalence rates as low as 44 in rural areas and as high as 842 per 100000 among the urban Parsi community in Mumbai (3). Studies conducted across many regions of India indicate that stroke accounts for two percent of hospital registrations and 9 to 30 percent of neurological admissions (4, 5). There are many risks factors for stroke including age, sex, family history of stroke, hypertension, smoking, diabetes, hyperlipidemia, atrial fibrillation (6–12).

Homocysteine is a sulphur containing amino acid derived from the metabolic demethylation of dietary methionine. There are studies which have shown a correlation between elevated hemocysteine and the risk factor for atherosclerotic vascular disease

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(13–17) while one study has put the role of homocysteine in atherosclerosis into question (18). Similarly, many of the studies have shown relationship of homocysteine with stroke (19–21) but some could not find the correlation (22–23).

The present study was planned to estimate serum homocysteine levels in patients with ischemic stroke and to compare these with levels of homocysteine in controls, and to find the relationship, if any, between serum homocysteine levels and risk of ischemic stroke.

MATERIAL AND METHODS

The study was carried out in the department of Biochemistry and Medicine, Dayanand Medical College & Hospital, Ludhiana. It was planned to study 100 cases of ischemic stroke and 100 control subjects. However at the end of study, there were 117 subjects of ischemic stroke (Group A) and 101 subjects in group B (controls). All the cases presenting in the department of Medicine were screened and cases of stroke fulfilling the inclusion criteria were included in the study which was : (i) First ever episode of ischemic stroke (ii) Cases presenting within two weeks of the event (iii) Age above 26 years.

The patients were excluded from the study who had non ischemic cause of stroke (traumatic, arterial dysfunction, hemorrhage) and embolic stroke, renal, hepatic, thyroid dysfunction, cancer, smokers and chronic users of anticonvulsant drugs. Control subjects were taken from outpatient facility as well as indoor patients without any evidence of stroke, coronary artery disease and peripheral vascular disease.

All the subjects included in the study were subjected to thorough history and clinical examination. They were evaluated for risk factors like hypertension, diabetes mellitus and hyperlipidemia. The investigations which were carried out included: Hemogram, blood sugar, renal, hepatic and thyroid function tests, urine routine examination, chest roentgenogram, electrocardiogram, CT/MRI head in stroke patients.

Overnight fasting blood samples were collected for lipid profile and homocysteine levels. Lipid profile (including total, HDL and LDL-cholesterol, triglycerides) were processed on Multi-channel Autoanalyser (Hitachi-911) using kits from Roche Ltd.

Total L-Homocysteine in serum was estimated by Microplate enzyme immunoassay using kits from Biorad Ltd. The controls (low, medium, high) of homocysteine were processed alongwith.

To compare mean values of homocysteine and other variables in patients of both groups, Student't' test was performed while test of proportions (Z-test) was performed wherever proportion of subjects in the two groups was compared. Chi Square test was conducted to check the association between two qualitative variables. To find the significant association between two variables Karl Pearson coefficient of correlation's was calculated.

RESULTS

All the subjects were in the age range of 26 to 80 with mean (±S.D.) age in group A were 59.54±11.59 years and group B as 56.59±13.01 years. Out of 117 patients in group A (ischemic stroke) 75 patients were males and 42 were female and out of 101 subjects in group B (control) 76 were males and 25 females (Table I). In group A, 42 patients had diabetic mellitus while 75 were non-diabetic. In group B, 33 had diabetes mellitus and 68 were non-diabetic. 68 patients in group A had hypertension and 49 were non-hypertensive. In group B, there were 54 hypertensive and 47 were non-hypertensive (Table II).

The results of lipid profile are presented in Table III. Total cholesterol, LDL-cholesterol and triglycerides were significantly higher in patients with ischemic stroke when compared to controls.

Serum homocysteine was high in group A (Ischemic stroke) as compared to control group B (P<0.01) (Table III). Homocysteine levels showed no difference between males and females in both the groups. In diabetic and non-diabetic patients, the homocysteine levels remained non-significant (Table IV). In patients with hypertension in Ischemic stroke group, homocysteine levels were significantly higher when compared to non-hypertensive patients (P<0.05) Correlation of homocysteine with age was statistically insignificant (P>0.10). Similarly, correlation of homocysteine with various parameters of lipid profile in patients with ischemic stroke was non-significant (P>0.10). But, in control group, homocysteine levels showed positive and significant correlation with total cholesterol and triglyceride levels (Table III).

TABLE I : Mean age & sex distribution.

| Group | Age (yrs) | Sex distribution (%) | |
		Male	Female
A	59.54±11.59	64.1	75.25
B	56.59±13.01	35.9	24.75

TABLE II : Incidence of diabetes & hypertension.

Group	Diabetes (%)	Hypertension (%)
A	35.9	58.1
B	32.67	53.47

TABLE IV : Homocysteine levels in diabetes and hypertensive patients.

| Patient | Mean homocysteine levels (umol/L) | |
	A	B
Diabetic	16.52±7.62	11.42±4.5*
Non diabetic	16.95±6.25	12.72±4.75*
Hypertensive	18.01±6.96	12.44±4.95*
Non hypertensive	15.11±6.1	12.14±4.38*

*P<0.01

TABLE III : Lipid profile and homocysteine levels in patients with ischemic stroke and controls (Mean±S.D.).

Group	Total cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dL)	Triglycerides (mg/dL)	Serum homocysteine (umol/L)
Ischemic stroke (n=117)	190.36±39.42*	42.67±8.30	107.54±33.45*	206.32±81.67*	16.80±6.71*
Controls (n=101)	165.07±33.51	43.47±14.85	88.09±25.57	117.08±54.39	12.30±4.68

*P<0.01

DISCUSSION

There is growing evidence that elevated levels of homocysteine play an important role in atherosclerotic disease (24). Hyperhomocysteinemia promotes oxidative damage by Reactive Oxygen Species (25), and cause smooth muscle proliferation. The high prevalence of hyperhomocysteinemia makes it an ideal target for intervention in patients with vascular disease as well as in general population. Homocysteine has been postulated as an independent risk factor for stroke (17, 26, 27). The increased risk of stroke in patients with hyperhomocysteinemia is due to its plausible role in the pathogenesis of atherosclerosis. Homocysteine has the adverse influence on the endothelial surface. There is a complex interplay of the oxidative product of homocysteine with vascular smooth muscle cells, connective tissue, plasma lipoproteins, clotting factors and platelets. The homozygotes for the three distinct autosomal recessive inborn errors of homocysteine metabolism (cystathionine β synthase deficiency. Methylene-tetrahydrofolate reductase deficiency and the cobalamin metabolic defects that impair methonine synthase activity) have high homocysteine concentration and a very high risk of premature atherothrombotic vascular disease (28, 29).

An association between elevated homocysteine and stroke has been postulated which may be due to acute vascular events themselves (29).

A few studies have shown that homocysteine levels increase with age (30, 31). This correlation is explained on the basis of nutritional status, vitamin intake which is likely to deteriorate with increase in age. In another study, no correlation was found between homocysteine levels and age. In our study also, there was no significant relationship between homocysteine levels and age. In one of the study, males were found to have higher homocysteine levels than females (31). However, in the present study, the difference between males and females was statistically insignificant.

There has been inconsistent data regarding relation between homocysteine and hypertension. Some could not find the correlation (32) while other have reported relationship between hypertension and homocysteine levels. In our study, the homocysteine levels were higher in hypertensive subjects in ischemic stroke as compared to non-hypertensive subjects. Homocysteine may alter the vascular endothelial function and promote hypertension. Similarly, inconsistent results have been found as far as correlation between homocysteine levels and diabetes mellitus (27, 35). Some of the workers could not find association between homocysteine and lipid profile while others reported a definine correlation. In the present study, a positive correlation between total cholesterol, LDL-cholesterol, triglycerides with homocysteine levels was found, which was significant in controls but insignificant in ischemic stroke patients.

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