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ASSOCIATION BETWEEN ISCHEMIC STROKE AND HOMOCYSTEINE

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Abstract:
Background: *Epidemiological studies have identified hyperhomocysteinemia as a possible risk factor for atherosclerosis. The aim of the study was to assess the relationship between homocysteinaemia and patients with ischemic stroke.*
Methods and Materials: *This was a prospective observational study conducted at the Neurology department and Medicine Unit-II of Services Hospital, Lahore for one-year duration from May 2019 to April 2020. Thirty-six consecutive ischemic stroke patients were analyzed for total homocysteine, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, and an equal number of age-matched controls were compared to a group of cases.*
Result: *The mean fasting blood sugar level, fasting total cholesterol (TC) in the serum, and low-density lipoprotein (LDL) in the serum were significantly higher in the group of patients (p = 0.001). Serum TC and LDL levels correlated positively with serum homocysteine (p = 0.001). High-density lipoprotein (HDL) in serum showed a negative correlation (p = 0.718), and serum triglycerides (TG) had a negative correlation (p = 0.182). The total level of fasting homocysteine in the group of patients was 21.89 ± 9.38 µmol / L, and in the control group it was 12.31 ± 3.27 µmol / L (p = 0.001). Elevated levels of fasting homocysteine were found in 75.0% of patients with ischemic stroke and in 16.67% of healthy subjects (p = 0.001). The incidence of hyperhomocysteinemia is higher in ischemic stroke than in age and sex-matched healthy controls.*
Conclusion: *In our study, hyperhomocysteinemia in patients with ischemic stroke was identified as a vascular risk factor. A significant correlation was found between the concentration of homocysteine and ischemic stroke.*
Key words: *homocysteine, carotid stenosis, ischemic stroke*

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INTRODUCTION:

Stroke is a global health problem. It is the leading cause of morbidity, mortality and disability in developed and developing countries[1-2]. Hyperhomocysteinemia is associated with premature disease of the peripheral, cerebrovascular and coronary vessels. Hyperhomocysteinemia has been identified as associated with vascular disease, including cerebrovascular disease[3-4]. Many follow-up and cohort studies have identified a strong, independent and dose-dependent association between moderately elevated homocysteine levels and atherosclerotic vascular disease, including stroke[5-6]. In this study, we undertook a prospective clinical trial of consecutive hospitalized patients with their first ever ischemic stroke and it was specifically investigated whether there could be an association between homocysteine, serum lipid profile and ischemic stroke[7-8]. The current study investigated the association of serum homocysteine with ischemic stroke.

METHODS:

This was a prospective observational study conducted at the Neurology department and Medicine Unit-II of Services Hospital, Lahore for one-year duration from May 2019 to April 2020. 36 consecutive male and female patients admitted with a diagnosis of acute ischemic stroke and compared them with 36 controls of age matched volunteers from the outpatient clinic. The inclusion criteria for the study were as follows: (1) with neurological examination and neuroimaging (CT / MRI), the diagnosis of ischemic stroke was strictly verified within 48 hours, (2) no impairment of liver, kidney and endocrinology, (3) no systemic malignancies , (4) people who are not taking any preparations containing vitamin B12 and folic acid or any drugs with an antimetabolite effect, such as methotrexate or phenytoin etc. Stroke was defined as a clinical syndrome characterized by rapidly developing clinical symptoms and / or focal symptoms, and sometimes general loss of brain function, with symptoms lasting> 24 hours or leading to earlier death and with no apparent cause other than vascular origin. All patients were examined by a neurologist and had tomography (CT) or magnetic resonance imaging (MRI). Clinical information including age, gender, history or current evidence of hypertension (HT) [systolic blood pressure (SBP) e "150 mmHg and diastolic BP e" 90 mmHg], diabetes mellitus (DM) [fasting blood glucose 3, 5-5.5 mmol / L] heart disease was recorded for all patients. In the case of venous blood samples were taken after their admission and from the controls from the outpatient clinic in the morning after an overnight fast for at least 12 hours in EDTA tubes. Total serum cholesterol, HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), VLDL cholesterol (VLDL-C), and triglycerides were measured using standard enzyme procedures. Normal limits are total cholesterol <5.2 mmol / L, HDL-C> 1.0 mmol / L, LDL-C <3.0 mmol / L, VLDL <1.1 mmol / L and triglycerides <2.3 mmol / l. Total plasma homocysteine levels were measured in the patients in the first 48 hours after the onset of stroke. Plasma homocysteine levels were determined by FPIA (Polarized Fluorescence Immunoassay) on the Abbott AxSYM System. Kit supplied with AxSYM Germany. The manufacturer's and laboratories upper limit was 15 mmol / L. Values above 15 mmol / L were acceptably high. Statistical analyzes related to this study were performed using the SPSS13 package. Descriptive statistical methods (mean, standard deviation) were used during the evaluation of the collected data; In addition to these methods, the free Student's t-test was used for pairwise comparisons between groups, using non-parametric tests taking into account the number of patients in groups consisting of the classification of patient groups by etiology. The chi-square test was used for comparisons between groups, which was used for comparisons between qualitative data. Correlations between numerical variables such as cholesterol, triglycerides and homocysteine were tested using the t-test. The results of these tests were set at a significance level of $p < 0.05$ and a confidence interval of 95%.

RESULTS

The study included 36 patients with ischemic stroke (18 women and 18 men) and 36 people from the control group (18 men and 18 women). The mean age of the group of patients was in the range of 50.28 ± 14.29, and the mean age of the control group was 51.08 ± 14.50 (Table 1).

Table-I: ***Distribution of age by group***

Age (in year)	Group		p value*
	Case	Control	
≤30	3 (8.3) #	4 (11.1)	
30-50	17 (47.2)	15 (41.7)	
50-70	14 (38.9)	15 (41.7)	
>70	2 (5.6)	2 (5.6)	
Total	36 (100.0)	36 (100.0)	
Mean ± SD	50.28 ± 14.29	51.08 ± 14.50	0.813

In terms of risk factors for HT, ischemic heart disease (CAD), DM was characterized by significantly higher incidence rates in the patient population. In the group of patients, only HT was significantly higher in the Case group in terms of the distribution of risk factors in etiological subgroups (p = 0.0.230); no significant difference was identified.

Table-II: ***Distribution of history of risk factors by group***

Risk factors	Group		p value*
	Case	Control	
Hypertension(HT)	17 (47.2)#	12 (33.3)	0.230
Ischemic heart disease(IHD)	7 (19.4)#	6 (16.7)	0.759
Valvular heart disease	2 (5.6)#	0 (0.0)	0.151
Diabetes mellitus(DM)	9 (25.7)#	8 (22.9)	0.780

(Table II) Mean, Standard Deviation of Fasting Total Cholesterol, Triglycerides, HDL-C, LDL-C, and VLDLC in Patients and Controls are summarized in Table 3.

Table-III:

Fasting blood sugar, serum fasting lipid profile and fasting total plasma homocysteine level by group

Parameter	Group		P value*
	Case(n=36)	Control(n=36)	
Fasting blood sugar (mmol/l)	8.30 ± 3.82	5.87 ± 1.77	0.001
Total Cholesterol (TC) (mg/dl)	207.14 ± 56.52	166.69 ± 28.55	0.001
HDL (mg/dl)	35.94 ± 15.95	39.14 ± 18.27	0.432
LDL (mg/dl)	137.06 ± 57.21	93.13 ± 26.44	0.001
Triglyceride (TG) (mg/dl)	205.19 ± 77.03	183.19 ± 60.60	0.182
Total plasma homocysteine level(fasting) (mmol/l)	21.89 ± 9.38	12.31 ± 3.27	0.001

There was no statistical difference between the two groups. Compared to controls, the mean fasting plasma homocysteine level was significantly higher (p <0.01). While the homocysteine level was found to be normal in 25% of the patients, it was found to be elevated in 75%. It was found that the homocysteine level in the control group was within the normal range in 83.33% of the controls; and only 16.67% of the controls showed elevated levels of homocysteine.

Table-IV

Distribution of respondents according to level of homocysteine by group

Homocysteine	Group		Total	p value*
	Case (%)	Control (%)		
Normal	9(25.0) #	30 (83.33)	46 (63.89)	0.0.001
Elevated	27 (75.0)	6 (16.67)	26 (36.11)	
Total	36 (100.0)	36 (100.0)	72(100.00)	

(Table IV) In determining the correlation between the level of homocysteine and the level of lipids in the group of patients, serum TC and LDL showed a positive correlation with the level of homocysteine in the serum with a p value of 0.001. Serum HDL correlated negatively with a p-value of 0.718, and TG had a positive p-value of 0.205. (Table 5)

Table-V

Correlation between serum fasting lipid profiles with total plasma homocysteine level

Serum fasting lipid profiles	r value	p value
TC(mg/dl)	0.388	0.001
HDL(mg/dl)	-0.043	0.718
LDL(mg/dl)	0.416	0.001
TG(mg/dl)	0.151	0.205

DISCUSSION:

The purpose of this study was to determine the correlation between plasma homocysteine levels and stroke, and to discover the association between elevated plasma levels and lipid levels and ischemic stroke. Elevated levels of total homocysteine (tHcy) in plasma have been identified as a risk factor for coronary heart disease, ischemic stroke and peripheral arterial disease, but most of these findings were from the white population and it is not known whether whether such findings also apply to Asians. The mean age of the patients was 50.28 ± 14.29 years and the controls 51.08 ± 14.50 years, with no significant difference between the two groups. Most of the subjects belonged to the age group of over twenty to eighty years[8-9]. In a previous study of the same type investigating the association of homocysteine with ischemic stroke, the mean age was 66 years, and in another study, it was 66.2 ± 11.0 years. Diabetes mellitus, hypertension and coronary heart disease, family history of hypertension and diabetes mellitus, smoking are considered important risk factors for stroke[10-11]. In some limited trials, no association with known risk factors has been established. Several studies have found that elevated homocysteine levels are significantly correlated and associated with smoking, male gender, hyperlipidemia, and hypertension. In the present study, mean fasting serum sugar, fasting lipid profile (TC), and serum LDL were significantly higher among the cases, but HDL and serum triglycerides (TG) did not show such a difference. In the series of mean (± standard deviation) of total cholesterol, triglycerides, HDL-C, LDL-C, and VLDL-C in patients and the pooled controls, no statistical difference was found. Hyperhomocysteinemia defines elevated homocysteine levels as exceeding 15.8 mmol per liter (95th percentile for healthy controls). Others defined the elevated homocysteine concentration as exceeding 13.9 mmol per liter (mean plus 2 SD among healthy young controls)[12-13]. In the Framingham Heart Study group, the cohort previously considered a homocysteine concentration of 14 mmol per liter per liter, which should be increased (90th percentile for people with apparently adequate levels of folic acid, vitamin B12 and vitamin B6). In the present study, the total level of fasting plasma homocysteine in the group of patients was 21.89 ± 9.38 µmol / l, which was significantly higher than in the control group (12.31 ± 3.27 µmol / l), (p = 0.001). In the series, the median total homocysteine concentration was 16.4 mmol / L among the cases compared to 14.3 mmol / L in the control group. Total homocysteine concentrations were higher in 2/3 of matched pairs. In the present study 25.0% of cases total serum homocysteine levels were normal and were elevated in 75.0% of cases. In the control group, 83.33% of the respondents were within the normal range, and 16.67% were elevated. The level of homocysteine was significantly higher

among the cases (p = 0.001). In a recent study, homocysteine levels were normal in 35.4% of patients, found slightly elevated in 56.3% of patients and moderately elevated in 8.3%. The homocysteine level in the control group was found to be within normal limits for 90% of the controls; and only 10% of controls showed slightly elevated levels of homocysteine (p <0.01)[14]. In the study, total homocysteine levels were normal in 71.5% of stroke cases and increased in 28.5% 26. Total serum cholesterol (TC), LDL correlated positively with serum homocysteine with a p value of 0.001. Serum HDL correlated negatively and TG was positive without statistical significance. Fujishama reported that as a manifestation of lacunar infarction, it is the most common type of ischemic stroke compared to Japanese people with elevated levels of homocysteine in particular, with a stroke caused by atherosclerosis[15]. Although Mousavi et al did not find any significant difference in homocysteine-associated atherosclerosis in the Asian population.

CONCLUSION:

The current study found that higher levels of homocysteine are significantly associated with ischemic stroke, and that hyperhomocysteinemia is an independent risk factor for ischemic stroke.

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