

Association Between Homocysteine And Stroke Severity

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Abstract: Stroke is one of the leading causes of death and disability throughout the world. The incidence of this disease is increasing with the gradual increase in obesity, diabetes mellitus, hyperlipidemia, hypertension and other cardiac problems. Hyperhomocysteinemia has also been proposed as an important risk factor for stroke especially ischemic stroke. This study was aimed to evaluate the homocysteine levels in ischemic stroke patients in comparison to apparently healthy controls and to explore the association between homocysteine and stroke severity (assessed by NIHSS scoring).

Materials And Methods: Study included 30 patients of ischemic stroke and 20 apparently healthy controls. Plasma homocysteine and serum lipid profile were estimated in all individuals. NIHSS and GCS scoring was done in all patients.

Results: The mean value of homocysteine ($\mu\text{mol/L}$) (47.34 ± 17.35) was significantly higher in cases when compared to controls (7.28 ± 3.65) ($p < 0.0001$). The median of LDL cholesterol was significantly higher in patients when compared to controls. [Median (mg/dl) (range) {Patients-94.5(30-166) vs controls 73(24-95) $p = 0.0068$ }. The median of total cholesterol, VLDL and Triglycerides was higher in cases as compared to controls, but the difference was not significant. Homocysteine in patients had shown a significant positive correlation with NIHSS score ($r = 0.51$, $p = 0.0039$) and volume of infarct ($r = 0.39$, $p = 0.03$) and significant negative correlation with GCS ($r = -0.42$, $p = 0.02$).

Conclusion: Homocysteine correlated well with severity of ischemic stroke.

Keywords: Homocysteine, ischemic stroke, NIHSS.

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I. Introduction

Stroke is a heterogeneous condition and its subtypes have different pathophysiological mechanisms and etiologies. Despite a gradual decline in overall stroke death rates in many industrialized countries, stroke remains a leading cause of death and disability in the world [1]. The incidence of this disease is increasing with the gradual increase in obesity, diabetes mellitus, hyperlipidemia, hypertension and other cardiac problems. Hyperhomocysteinemia has also been proposed as an important risk factor for stroke especially ischemic stroke. Homocysteine (HCY) is associated with risk of stroke, but whether HCY affects stroke severity remains controversial. We hypothesized HCY has an impact on atherothrombosis and this study was aimed to evaluate the homocysteine levels in ischemic stroke patients in comparison to apparently healthy controls and to explore the association between HCY and stroke severity.

II. Materials And Methods

This is a cross sectional case control study. Study included 30 patients of ischemic stroke and 20 apparently healthy controls. All the patients above 20 years of age attending to our hospital, with clinically and radiologically diagnosed as stroke were included in the study. Patients were excluded if they had history of alcoholism, smoking or other drug abuse, psychiatric disease, pernicious anaemia, stomach or bowel disease, bowel surgery, chronic renal failure or liver disease and also vegetarians.

2.1 Clinical Assessment:

Thorough clinical history was taken about the onset and duration of stroke. Details about various risk factors for stroke like hypertension, smoking were noted. Past history of any stroke or transient ischemic attack (TIA) was also considered. CT, MRI, MRA or DWI was done to confirm the diagnosis and volume of infarct was noted. NIHSS (National Institutes of Health Stroke scale) and GCS (Glasgow coma score) scoring were done for all stroke patients.

2.2 Biochemical Investigations:

Fasting venous blood samples were collected for the estimation of plasma homocysteine (by chemiluminescence method) and serum lipid profile (total cholesterol, HDL-Cholesterol, Triglycerides by enzymatic colorimetric method.LDL-Cholesterol was calculated by Friedewald’s equation (LDL-Cholesterol =Total Cholesterol-HDLCholesterol-triglycerides/5).

2.3 Statistical Analysis: Descriptive statistics of normally distributed variables is reported as mean and SD and that of non-normally distributed variables is reported as median and range.To test the differences between two groups (cases and controls) we used unpaired Student’s t-test for normally distributed variables and Mann Whitney U test for non-normally distributed variables. P< 0.05 was considered as statistically significant.

III. Results

3.1 Baseline characteristics:

Study included a total of 50 subjects, that included 30 ischemic stroke patients (males-24, females-6) and 20 healthy controls (males-15, females-5).The mean age was 51.17±8.49 years in cases group and 47.1±5.4 years in controls group.There was no statistical difference between the two groups (p=0.06) (Table 1)

3.2 Biochemical investigations :

The mean value of homocysteine (µmol/L) (47.34±17.35) was significantly higher in cases when compared to controls (7.28±3.65) (p<0.0001) (Table 1) (Figure 1) The median of LDL cholesterol was significantly higher in patients when compared to controls. Median(mg/dl)(range){Patients-94.5(30-166) vs controls 73(24-95) p=0.0068} (Table 1) (Figure 2) The median of total cholesterol, VLDL and Triglycerides was higher in cases as compared to controls, however the difference was not significant (Table 1) The mean of HDL cholesterol was lower in cases as compared to controls, however the difference was not significant (p=0.06)(Table 1) .

Table 1: Demographic variables in study groups.

| Variable | Controls (N=20) mean± SD, Median(Range) | Cases (N=30) mean± SD, Median(Range) | p value |
|-----------------------------------|---|--|-----------|
| Homocysteine (µmol/L) * | 7.28 ± 3.65 | 47.34 ±17.35 | <0.0001** |
| T.Cholesterol(mg/dl) [#] | 144 (85-195) | 155(85-243) | 0.06 |
| HDL-C (mg/dl) * | 48.3±12.98 | 42.37±8.88 | 0.06 |
| LDL-C (mg/dl) [#] | 73(24-95) | 94.5(30-166) | 0.0068** |
| VLDL (mg/dl) [#] | 18.5(11-36) | 22(8-63) | 0.06 |
| Triglyceride (mg/dl) [#] | 92.5 (56-181) | 111.5 (39-317) | 0.06 |

*Mean ± SD for normally distributed parameters whereas [#] median and ranges for non-normally distributed parameters. ** p<0.05 is considered significant.

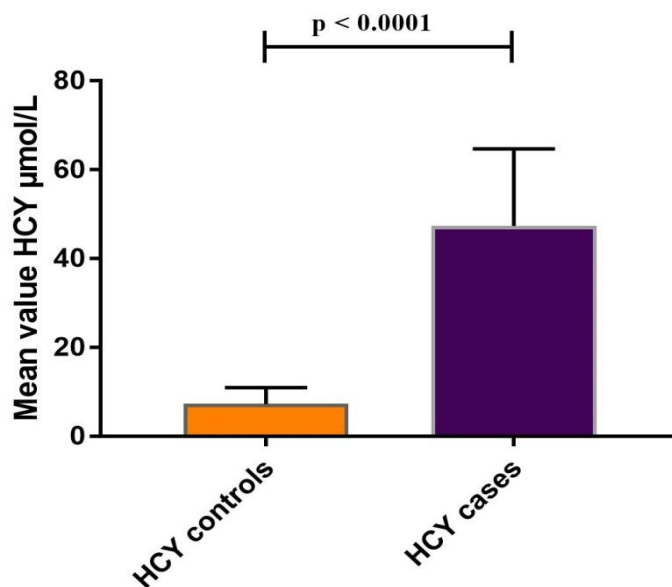


Figure 1 : Comparison of homocysteine in controls and cases

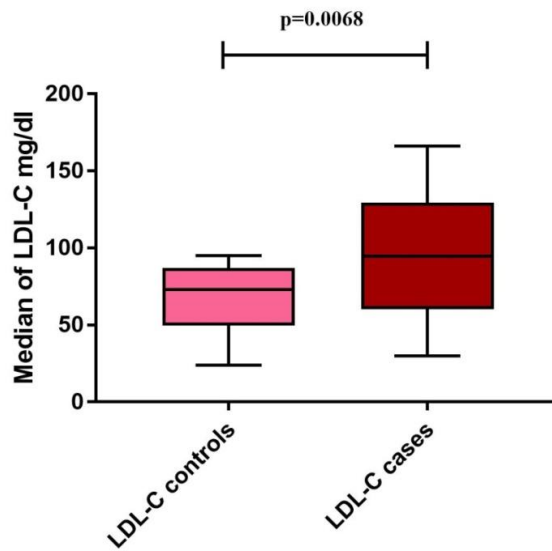


Figure 2 : Comparison of LDL cholesterol in controls and cases

Homocysteine in patients had shown a significant positive correlation with NIHSS score ($r=0.51$, $p=0.0039$) (Table 2) (Figure 3) and volume of infarct($r=0.39$, $p=0.03$) and significant negative correlation with GCS ($r = -0.42$, $p=0.02$).

Table 2: Correlation of homocysteine with different variables in ischemic stroke patients

| Variable | r value | p value |
|-------------------|---------|---------|
| NIHSS | 0.51 | 0.0039* |
| Volume of infarct | 0.39 | 0.03* |
| GCS | -0.42 | 0.02* |

* $p<0.05$ is considered significant

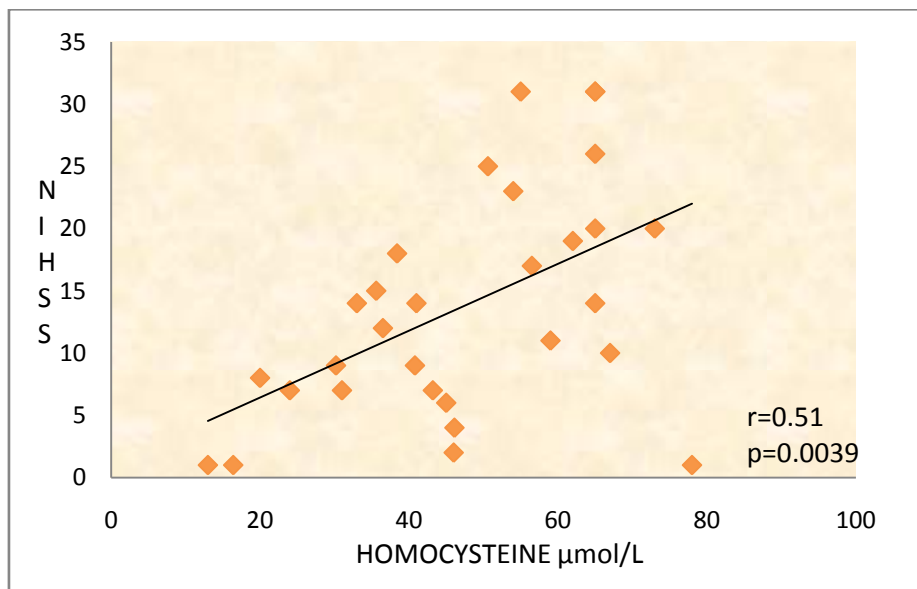


Figure 3: Correlation of Homocysteine with NIHSS in Ischemic stroke patients

IV. Discussion

In our study mean value of homocysteine was significantly higher in cases as compared to controls. M Modiet al [2] in their study on ischemic stroke patients found significantly higher levels of homocysteine in patients as compared to controls (9.91 ± 2.25 vs 8.00 ± 2.74 mmol/l; $P < 0.001$) which is in agreement with our study. Similarly the mean fasting Hcy levels was significantly higher in the cases ($16.2 \mu\text{mol/L}$, 95% CI: 14.8 to 17.5) than in the controls ($13.5 \mu\text{mol/L}$, 95% CI: 12.4 to 14.6) ($P=0.013$) in a study by NahidAshjazadeh et al

[3]. Tan et al [4] studied 109 young adult Asians (Chinese, Indians, and Malays) with ischemic stroke and found a strong relationship between increased Hcy and ischemic stroke (OR=5.17, 95% CI: 1.96 to 13.63; P=0.001). Other studies have reported the same results in Turkish and Malay populations with ischemic stroke [5,6] Furthermore, Biswas et al [7] conducted a study in 120 Indian patients with acute ischemic stroke and showed that there was a significant relationship between hyperhomocysteinemia and ischemic stroke (P=0.001). In our study homocysteine correlated well with severity of disease (assessed by NIHSS) ($r=0.51, p=0.0039$). Xu-Qing Wu et al also found that acute phase elevated HCY correlated with severity and prognosis in patients with atherothrombotic stroke [8].

Homocysteine (Hcy) is a four-carbon amino acid with a free thiol group, which is formed by demethylation of methionine, an essential amino acid derived from diet. Homocysteine causes oxidative damage to the vascular endothelium and stimulates proliferation of the vascular smooth muscle cells creating a prothrombotic condition, which contributes to the development of premature atherosclerosis. Homocysteine also inhibits several different anticoagulant mechanisms that are mediated by the vascular endothelium. It inhibits the expression and activity of endothelial cell surface thrombomodulin, the thrombin cofactor responsible for protein C activation. Homocysteine inhibits the antithrombin III binding activity of endothelial heparan sulfate proteoglycan, thereby suppressing the anticoagulant effect of antithrombin III. Homocysteine also inhibits the ecto-ADPase activity of human umbilical vein endothelial cells (HUVECS). Because ADP is a potent platelet aggregatory agent, this action of homocysteine is prothrombotic. Homocysteine also interferes with the fibrinolytic properties of the endothelial surface because it inhibits the binding of tissue plasminogen activator [9]. All these effects of homocysteine lead to an atherothrombotic state and significantly higher levels of homocysteine in ischemic stroke patients in our study can be explained by this fact.

In our study, the median of LDL cholesterol was significantly higher in patients when compared to controls. Median (mg/dl) (range) {Patients-94.5(30-166) vs controls 73(24-95) $p=0.0068$ }. The median of HDL was lower in cases as compared to controls, however the difference was not significant ($p=0.06$). Denti et al [10] reported that LDL-C concentrations over 100 mg/dl along with low HDL-C levels were associated with higher stroke risk. Uddin MJ et al [11] reported that high level of serum total cholesterol and LDL cholesterol showed significant risk in ischemic stroke ($p<0.05$). Our study has limitation due to the small sample size, its statistical power might be insufficient.

V. Conclusion

Our study concludes that higher levels of homocysteine is associated with risk of ischemic stroke and the levels of homocysteine are indicative of stroke severity. This indicates the need of estimation of plasma homocysteine on routine basis for patients at risk. These findings merit further research on a larger population so that it can be useful in clinical decision making.

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