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Study on Homocysteinemia as a Risk Factor of Ischemic Stroke

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Abstract

Despite recent advances, only two-third of all strokes can be attributed to known causal risk factors. Homocysteine (tHcy), a sulfur-containing amino acid, is now considered to be an important risk factor for vascular diseases, along with the established risk factors like hyperlipidemia, hypertension, diabetes mellitus, and smoking. Elevated homocysteine levels play a causal role in the pathogenesis of atherosclerosis, thromboembolism and vascular endothelial dysfunction with an increased incidence of ischemic stroke.

This study aimed to find out the association of hyperhomocysteinemia with ischemic stroke. A total of 100 subjects were included in this study, 50 were ischemic stroke patients enrolled as case, and 50 were normal healthy individuals enrolled as control. Serum homocysteine level was measured in both case and control groups. The comparison was made in both groups regarding other common risk factors like diabetes mellitus, hypertension, smoking, dyslipidemia, family history, etc.

Among 100 patients, 50 had ischemic stroke and 50 were healthy individuals. In this study, out of all patients, abnormal serum homocysteine level was found in 32% of cases and 12% of controls. The mean (±SD) serum homocysteine level was found 16.50±13.86 µmole/L in cases and 9.46±3.49 µmole /L in the control group. Significant ($p<0.05$) difference was found between the case and the control. The incidence of hyperhomocysteinemia is higher in ischemic stroke cases than that in age-sex-matched healthy controls. In our study, serum homocysteine was high in both younger age group patients (16.65±14.55 µmole/L vs. 9.52±3.19 µmole/L) and older age group patients (16.33±9.87 vs. 9.35±3.97 µmole/L,) in case and control group respectively. Significant ($p<0.05$) difference was found between the case and the control. Multiple logistic regression analysis showed that abnormal serum homocysteine is an independent risk factor of ischemic stroke. So we conclude that hyperhomocysteinemia is an important and independent risk factor for the development of ischemic stroke. Hypertension and smoking are important contributory to elevated serum homocysteine.

Keywords: Homocysteinemia, ischemic stroke, modifiable risk factors.

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Introduction

World health organization (WHO) defined stroke as a clinical syndrome occurring due to sudden cerebral dysfunction, producing focal or global neurological deficit, persisting for more than 24 hours, or the patient dies within 24 hours, vascular in origin, non-epileptic, non-traumatic in nature.[1] About 85% of stroke is caused by primary

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cerebral ischemia resulting in infarction (ischemic stroke), and 15% are caused by cerebral hemorrhage (hemorrhagic stroke).[2]

Stroke is one of the foremost causes of morbidity and mortality throughout the world, posing a major socio-economic challenge in occupational and neuro-rehabilitation programs for stroke survivors. Numerous risk factors for stroke have been identified, and modification of these factors is the crux of primary and secondary prevention. Despite recent advances, only two-third of all strokes can be attributed to known causal risk factors.[3]

The commonest etiologies of ischemic strokes are atherosclerosis with thromboembolism and cardiogenic thromboembolism. The modifiable personal or social risk factors like hypertension, diabetes, obesity, and cigarette smoking triggers the incidence of cerebrovascular events, like stroke and TIA.[4] The modifiable biochemical risk factors like abnormal lipid metabolism, hypercholesterolemia, lipoprotein (a) [Lp(a)], hyperhomocysteinemia for an increased incidence of atherothrombotic cerebrovascular disease.[5]

There has been much interest in homocysteine (tHcy), a sulfur-containing amino acid, as an important risk factor for vascular diseases, including stroke, independent of the long-recognized factors like hyperlipidemia, hypertension, diabetes mellitus, and smoking.[6] Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine, an essential amino acid derived from dietary protein. It is metabolized with folate as a co-substrate, vitamin B_{12} as a co-factor, and the help of several enzymes.[7]

Hyperhomocysteinemia recently has been recognized as an easily modifiable risk factor for the presence of atherosclerotic cerebrovascular or cardiovascular disease and hypercoagulability states.[8] Elevated homocysteine levels play a causal role in the pathogenesis of atherosclerosis, thromboembolism and vascular endothelial dysfunction with an increased incidence of ischemic stroke.[9] More than 20 cross-sectional and three prospective studies in young and middle-aged and elderly subjects have shown that high levels of homocysteine are associated with an increased risk of myocardial infarction and stroke.[10]

On this background, our study aims at comparing the occurrence of homocysteine levels in patients with cerebral ischemic stroke group, is to determine the role of homocysteine as a marker for ischemic stroke.

Materials and Methods

It was a case-control study carried out among the patients with ischemic stroke admitted into Neuromedicine and Medicine Units of Rajshahi Medical College Hospital between the periods of January 2016 – December 2017. Total of 100 patients were enrolled in the study that fulfilled both the inclusion and exclusion criteria. Total 100 subjects were included in this study; 50 were ischemic stroke patients enrolled as case, and 50 were normal healthy individuals enrolled as control. Serum homocysteine level was measured in both case and control groups. Initially, they were assessed by serum homocysteine level. Data were collected by face-to-face interview, physical examination, and investigations in a predesigned data collection sheet. The conditions of few patients were assessed over the telephone. Data were collected after taking the informed consent of the patient.

Results

The findings of the study are being presented here.

Table-I: Mean Distribution of serum homocysteine level (µmol/L) among the study subjects (n=100):

Serum homocysteine level (µmol/L)	Case (n=50) n (%)	Control (n=50) n (%)	P Value
1. Normal (<15 µmol/L)	34 (68.0%)	44 (88.0%)	
2. High (>15 µmol/L)	16 (32.0%)	6 (12.0%)	p<0.001
Mean ± SD	16.50±13.86	9.46±3.49	

The mean (±SD) serum homocysteine level was 16.50±13.86 µmol/L in case. In control, the mean (±SD) serum homocysteine level was 9.46±3.49 µmol/L. Significant (p<0.001) difference was found between case and control in unpaired t-test. High serum homocysteine level was found in 16 (32.0%) cases and 6 (12.0%) in controls. Normal serum homocysteine level was found in 34 (68.0%) cases and 44 (88.0%) in controls. Significant (p<0.001) difference was found between case and control in unpaired t-test.

Table-II: Association of age on serum homocysteine level (µmol/L) among the study subjects n=100):

Age in groups	Case(n=50) Mean ± SD	Control(n=50) Mean ± SD	p value
Younger age group **(**≤45 years**)**	16.65±14.55	9.52±3.19	0.003
Older age group **(** > 45 years**)**	16.33±9.87	9.35±3.97	

The younger age group of patients ≤45 years. The older age group of patients > 45 years

The above table shows serum homocysteine level was high in both younger age group patients (16.65±14.55 µmol/L vs.9.52±3.19 µmol/L) and older age group patients (16.33±9.87 µmol/L vs. 9.35±3.97 µmol/L) in the case and the control group respectively. It was observed that serum homocysteine level was higher in the younger age group of cases than in the older age group. Significant (p<0.05) difference was found between the case and the control in the ANOVA test.

Table-III: Association of sex on serum homocysteine level (µmol/L) among the study subjects (n=100):

Sex	Case(n=50) Mean±SD	Control(n=50) Mean±SD	p value
Male	17.83±13.70	9.80±3.08	**0.002**
Female	15.03±10.69	8.92±4.05	

Significantly higher level of serum homocysteine levels was noted in male patients compared to controls (17.83±13.70 µmol/L vs. 9.80±3.08 µmol/L) and female patients compared to controls (15.03±10.69 µmol/L vs. 8.92±4.05 µmol/L). In cases, serum homocysteine levels were higher in the male patients than in the females. Significant ($p<0.05$) difference was found between the case and the control in ANOVA test regarding sex difference in the case and the control group.

Table-IV: Association of major risk factors on serum homocysteine level (µmol/L) among the study subjects (n =100):

Risk factors	Case (n=50) Mean ± SD	Control (n=50) Mean ± SD	**p-value**
Hypertensive	16.71±9.81	8.06±1.78	**0.752**
Normotensive	16.29±14.43	9.54±3.56	**0.019**
Diabetic	13.23±11.42	7.49±.27	**1.00**
Non-diabetic	17.30±12.52	9.53±3.54	**0.001**
Smoker	21.99±15.32	9.61±1.64	**0.026**
Non-smoker	12.51±7.63	9.43±3.65	**0.788**
Dyslipidemia	10.67±2.79	6.91	**0.001**
Non-dyslipidemia	17.00±12.69	9.50±3.50	**0.001**
Positive family history	17.22±14.45	8.48±4.78	**0.367**
Without family history	16.08±11.15	9.56±3.37	**0.016**

In hypertensive subjects, the mean (±SD) serum homocysteine level was 16.71±9.811 µmol/L and 8.06±1.78 µmol/L in case and control group respectively. In smoker subjects, the mean (±SD) serum homocysteine level was 21.99 ±15.52 µmol/L and 9.61±1.64 µmol/L in the case and the control respectively. In diabetic subjects, the mean (±SD) serum homocysteine level was 13.23±11.42 µmol/L and 7.49 ±0.27 µmol/L in the case and the control respectively. In positive family history subjects, the mean (±SD) serum homocysteine level was17.22±14.45 µmol/L and 8.48±4.78 µmol/L in the case and the control respectively. Among stroke patients, serum homocysteine level was higher in hypertensive patients, in patients with positive family history and in smokers than their normal counterparts. Statistically significant ($p<0.05$) difference was found among stroke patients regarding presence or absence of hypertension and smoking habit on serum homocysteine level.

Significant ($p<0.05$) difference was found between the case and the control in ANOVA test in normotensive, non-diabetic, smoker, dyslipidemic, and non-dyslipidemic groups regarding presence or absence of major risk factors on serum homocysteine level in the case and the control group.

Table-V Risk factors analysis for ischemic stroke (multiple logistic regression models) (n =100):

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
							Lower	Upper
Homocysteine	-.144	.071	4.147	1	.042	.866	.754	.995
DM	-2.595	1.021	6.454	1	.011	.075	.010	.553
HTN	-2.683	.803	11.154	1	.001	.068	.014	.330
Smoking	-1.720	.722	5.680	1	.017	.179	.044	.737
Dyslipidemia	-1.759	1.509	1.358	1	.244	.172	.009	3.317
Family History	-2.428	.744	10.653	1	.001	.088	.021	.379
Constant	3.496	.914	14.644	1	.000	32.993		

In multiple logistic regression analysis, ischemic stroke was the dependent variable; serum homocysteine level was the independent variable and hypertension, dyslipidemia, diabetes, positive family history and smoking as the covariates. Serum homocysteine level may found to be an independent predictor of ischemic stroke (OR=0.866, p<0.042, 95% CI=0.754-0.995) as well as DM (OR=0.075, p<0.011, 95%CI=0.010-0.553), HTN (OR=0.068 p<0.001 95% CI=0.014-0.330),smoking (OR=0.179 p<0.017,95% CI=0.044-0.737), dyslipidemia (OR=0.172 p<0.244, 95% CI=0.009-3.317), positive family history(OR=0.088 p<0.001, 95%CI = 0.021-0.379).

Discussion

The precise mechanisms underlying the apparent adverse effect of hyperhomocysteinemia on the risk of ischemic stroke are not clear at present, although several possibilities can be proposed. Hyperhomocysteinemia may cause a rise in arterial blood pressure, thereby increasing the risk of ischemic stroke.[11] Homocysteine alters the normal anti-thrombotic phenotype of the endothelium by enhancing the activity of factor xii [12] and factor v and depressing the activity of protein C.[13] Homocysteine also inhibits the expression of thrombomodulin, induces the expression of tissue factors[14], and suppresses the expression of heparin sulfate by the endothelium.[15]

In this study out of all patients, abnormal serum homocysteine level was found in 32% of cases and in 12% of controls. The mean (±SD) serum homocysteine level was found 16.50±13.86 µmol/L in cases and 9.46±3.49 µmol /L in the control group. Significant (p<0.05) difference was found between the case and the control.

Aminur et al. determined the relationship between Homocysteine and Ischemic Stroke in Bangladesh. They observed total plasma homocysteine level in the case group was 21.89±9.38 µmol/L and the control group was 12.31±3.27 µmol/L (p=0.001).[16] Elevated homocysteine level was found in 75.0% of ischemic stroke patients and in 16.67% of healthy controls (p=0.001). The incidence of hyperhomocysteinemia is higher in ischemic stroke cases than that in age-sex-matched healthy controls, which is consistent with our result.

Prashant et al. had undertaken a study of plasma homocysteine level as a risk factor for ischemic strokes in young patients in India. They observed total homocysteine level in the case group was 30.10±14.8 µmol/L and the control group was 13±5.3 µmol/L (p=0.001).[17] Elevated homocysteine level was found in 76.66% of ischemic stroke cases and in 10% of healthy controls (p=0.001).

Venkata et al. had undertaken a study of Homocysteine as an Independent Risk Factor for Cerebral Ischemic Stroke in South Indian Population in Rural Tertiary Care Centre. They observed the mean homocysteine levels in cases was 17.58±10.3, statistically significant than controls 6.34±4.22 (p< 0.05).[18] Presence of hyperhomocysteinemia in 59 (41.8%) of cases and in 6 (4.25%) of controls, statistically significant than controls (p <0.05), which is consistent with our result.

Akpalu et al conducted a case-control study of Plasma Homocysteine as a Risk Factor for Strokes in Ghanaian Adults. They assessed mean homocysteine level in stroke cases of 40.7±9.5 µmol/l was significantly higher than 16.8±10.6 µmol/l in controls (p=0.001).[19] There was a significant association of hyperhomocysteinemia with stroke (p=0.001).

Narang et al. showed a higher concentration of serum homocysteine level in ischemic stroke patients. They observed the mean serum homocysteine level was 16.80±6.71 µmol/L in ischemic stroke patients and in control it was 12.03±4.68 µmol/L.[20] The difference was statistically significant (p<0.05).

Alkali et al determined the relationship between plasma homocysteine and ischemic stroke in the Nigerian population, they observed the mean plasma homocysteine was significantly higher in ischemic stroke cases than in control subject (mean± SD: 20.8±10.2 µmol/L vs 13.1±4.5 µmol/L, p value<0.001).[21] All these finding were consistent with the result of the present study.

Modi et al., in a case-control prospective study, assessed hyperhomocysteinemia as a risk factor for ischemic stroke. They observed that the tHcy were significantly high in patients with stroke, compared to controls (9.91±2.25 µmol/L vs. 8.00±2.74 µmol/L; P < 0.001).[22]

Multiple logistic regression analysis was performed, where ischemic stroke was the dependent variable; the serum homocysteine was the independent variable and hypertension, dyslipidemia, family history of cardiovascular risk factor and smoking as the covariates. Results showed that abnormal serum homocysteine is an independent risk factor of ischemic stroke along with hypertension, family history of cardiovascular risk factor, and smoking.

Conclusion

From our findings, we conclude that Hyperhomocysteinemia is an important and independent risk factor for the development of ischemic stroke. Hypertension and smoking are important contributory for elevated serum homocysteine.

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