

# Frequency of Elevated Homocysteine Level in Patients Presented with Ischemic Stroke

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## ABSTRACT

**Background:** A stroke is the rapidly developing focal or global neurological deficit due to disturbance in the blood vessels supplying to the brain. There is increasing proof that increased homocysteine concentration may act as independent risk factor for ischemic stroke. So, this study was done to find the elevated homocysteine in stroke patients. **Objective:** To determine the frequency of elevated homocysteine levels in patients presenting with ischemic stroke. **Study Design:** Cross sectional study. **Settings:** Department of Neurology, Mayo Hospital, Lahore, Pakistan. **Duration:** Six months from March to August 2011. **Methodology:** Patients detailed medical history, physical examination and demographics were stored electronically, moreover the blood samples were drawn under aseptic measures within 24 hours of stroke. For each patient, homocysteine level was assessed through standard procedures from the blood. Data was analyzed through SPSS version 20 and entered in Proforma. **Results:** Mean age of patients was  $45.09 \pm 5.36$  years. Majority of the patients were male. 8(8.0%) patients were 20-30 years of age, 7(7.0%) patients were between 31-40 years old and 85(85%) patients were 41-50 years of age. Elevated homocysteine level was confirmed in 56 patients (56.0%). **Conclusion:** Homocysteine level was found to be frequently elevated in patients with ischemic stroke.

**Keywords:** Elevated homocysteine level, Ischemic stroke.

## INTRODUCTION

All over the world, stroke is one of the major cause of mortality and morbidity.<sup>1</sup> During 2010, the prevalence of stroke was 33million all over the world, and out of these, 16.9 million have first episode of stroke. Stroke is the 2<sup>nd</sup> leading cause of mortality all over the world after cardiovascular diseases, causing 11.13% of total mortality globally.<sup>2</sup> The current therapeutic strategy for management of acute ischemic stroke concentrates on restricting the level of brain injury, preventing complications after stroke, starting suitable secondary deterrence & expediting post-stroke repossession.<sup>3</sup> Most of the cases, particularly females, have non-traditional symptoms like general faintness, tiredness & altered consciousness which can help in early diagnosis.<sup>4</sup> Homocysteine is a thio-l amino acid synthesized during the metabolism of methionide increased plasma levels of homocysteine can be the result of genetic enzyme deficiencies of cystathionine  $\beta$ -synthase (CBS) and

methylene-tetra-hydrofolate-reductase (MTHFR).<sup>5</sup> Total homocysteine elevations above  $15\mu\text{mol/l}$  are an independent risk factor for ischemic stroke, whereas elevations of total homocysteine of  $10\text{-}15\mu\text{mol/L}$  less predictive.<sup>6</sup> According to a study elevated homocysteine level ( $>15\mu\text{mol/L}$ ) was 54% in patients of ischemic stroke. In the same study the mean homocysteine value among patients with elevated homocysteine level and with normal homocysteine level was observed as  $28.40 \pm 2.08\mu\text{mol/L}$  and  $11.16 \pm 1.09\mu\text{mol/L}$  respectively, which was highly significant (P value  $<0.001$ ).<sup>7</sup> Reduction in elevated homocysteine by as little as  $3\mu\text{mol/L}$  reduces the risk of stroke as 24%.<sup>8</sup> Aim of this study was to determine the frequency of elevated homocysteine level in patients presenting with ischemic stroke, moreover this study will set baseline data in our setup. This will ultimately benefits to the population by reducing the morbidity and mortality in patients of ischemic stroke that ultimately reduces the burden on hospital.

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## METHODOLOGY

**Study Design:** Cross sectional study.

**Settings:** Department of Neurology, Mayo Hospital, Lahore Pakistan.

**Duration:** Six months (from March to August 2011).

**Sample Technique:** Non-probability, purposive.

**Sample Size:** 100 patients, with 95% confidence level, 10% margin of error and taking expected value of elevated homocysteine level i.e., 54% in cases of ischemic stroke.

**Inclusion Criteria:** Both genders with the age of 20-50 years and diagnosed Patients with first episode of ischemic stroke (on CT scan) were included.

**Exclusion Criteria:** Patients having history of renal impairment (creatinine >1.5mg/dl), patients having drug history of drugs e.g., phenytoin, carbamazepine, HIV positive patients (assessed through history and lab investigation; Elisa), smokers (>5 pack year) and patients with vitamin B12 deficiency (<170pg/ml) were excluded.

**Data Collection Procedure:** Patient's demographic details including name, age, gender, were obtained, treatment of ischemic stroke was provided as per hospital protocol. Blood sample was drawn under aseptic measures within 24 hours of stroke with the help of BCC syringe by a staff nurse. Sample was sent to the hospital laboratory for the assessment of homocysteine level. From laboratory report serum total homocysteine was noted and if report of laboratory indicates that homocysteine level  $\geq 15\mu\text{mol/L}$ , then it was labeled as elevated. All information will be recorded on proforma.

**Data Analysis:** Data was analyzed by SPSS 20. Mean  $\pm$  SD was calculated for age and homocysteine level. Frequency distribution and percentages were calculated for qualitative variables like gender, elevated homocysteine level. P-values  $\leq 0.05$  was considered as significant.

## RESULTS

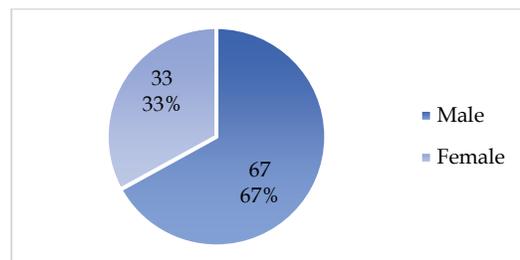
The mean age of patients was  $45.09 \pm 5.36$  years. The patient age was stratified later, out of which 8(8.0%) patients were 20-30 years of age, 7(7.0%) patients were between 31-40 years old and 85(85%) patients were 41-50 years of age (Table 1).

**Table 1: Age of patients**

Mean age	45.09 $\pm$ 5.36 years
20-30 years	8 (8%)
31-40 years	7 (7%)
41-50 years	85 (85%)
Total	100

Sixty-seven (67.0%) patients were male and 33(33.0%) patients were female (figure 1).

**Figure 1: Distribution of gender of patients**



The homocysteine level was elevated in 56 (56%) cases. While homocysteine level was normal in 44 (44%) cases. (Table 2).

**Table 2: Distribution of cases by homocysteine level**

Homocysteine level	Number	Percentage
Elevated	56	56.0%
Normal	44	44.0%
Total	100	100.0%

Among elevated homocysteine level, 36 were males while 20 were females. Among normal homocysteine level, 31 were males while 13 were females. The difference in both genders was insignificant for elevated homocysteine level. Similarly, among patients of age 21-30 years, there were more patients who had elevated homocysteine level, and similar pattern was observed in other age groups as well, although the difference was insignificant (p-value >0.05). But the patients who were diabetic, the chances of homocysteine level was significantly high than non-diabetic (p-value <0.05), similarly, in patients with elevated homocysteine level, there were more hypertensive and hyperlipidemia (p-value <0.05) and that may be the cause of stroke in patients with normal homocysteine level (Table 3).

**Table 3: Relationship of elevated homocysteine level with different effect modifiers**

		Homocysteine level		Total	P-value
		Elevated (n=56)	Normal (n=44)		
Gender	Male	36	31	67	0.5149
	Female	20	13	33	
Age (years)	20-30	5	3	8	0.9472
	31-40	4	3	7	
	41-50	48	37	85	
Diabetes	Yes	25	10	35	0.0226
	No	31	34	65	
Hypertensive	Yes	32	15	57	0.0219
	No	24	29	43	
Hyperlipidemia	Yes	35	17	62	0.0177
	No	21	27	38	

## DISCUSSION

Friedman evaluate homocysteine levels in 40 cases having atrial fibrillation; as after stroke, patients had elevated homocysteine level and were more aged than others, he proposed that elevated homocysteine levels detected in older patients may be an explanation for harsh rise in homocysteine level in stroke in cases of atrial fibrillation  $\geq 65$  years of age.<sup>9</sup> Analogous evidence was stated by Cingozbay *et al* in cases of atrial fibrillation.<sup>10</sup>

The present study, we determined the frequency of elevated homocysteine level in patients presented with ischemic stroke in 100 patients. Elevated level was observed in 56% of the patients which is highly consistent with the study carried out by Dhamiji *et al*.<sup>7</sup> The distribution of disease among gender is almost similar to the study by Narang *et al* these findings are close to our results where 67% were male while females were 33%. The referenced study also reported that homocysteine level was high in patients of Ischemic stroke as compared to patients without stroke ( $P < 0.01$ ).<sup>11</sup>

In our study, we found a significant relationship between homocysteine and age of patients where most common patients were in advance age group. In a study, it has been proved that men have high homocysteine levels as compared to females. But Wang *et al* reported that increased homocysteine concentration does not affect functional outcome in older patients after ischemic stroke ( $p > 0.05$ ).<sup>12</sup>

In our study, the patients who were diabetic, hypertensive or had hyperlipidemia had more chances of elevated homocysteine level than non-diabetic, non-hypertensive or had normal lipid profile ( $p$ -value  $< 0.05$ ). The patients, in whom stroke occurred but homocysteine level was normal, diabetes, hypertension and hyperlipidemia may be the cause of stroke.

Hyper-homocysteinemia stimulates oxidative injury by oversensitive oxygen kind and cause damage of smooth muscle.<sup>13</sup> The increased incidence of hyper-homocysteinemia marks it as ideal target for intrusion not only in cases of vascular diseases but also in general population. Homocysteine is hypothesized as independent risk factor for cerebrovascular accidents.<sup>14</sup> It is well-known that post-stroke neuronal injury causes over excretion of amino acids like glutamate & aspartate via stimulation of NMDA receptors. The brain come in contact with many plasma elements containing homocysteine as a consequence of disturbance in post-stroke blood-brain barrier, head trauma & anxiety.<sup>15</sup>

In patients of hyper-homocysteinemia, the high risk of stroke is because of its probable role in development of atherosclerosis. Homocysteine has adverse effects on endothelial surface. There is a difficult chemistry of oxidative product of homocysteine with cells of vascular smooth muscle, connective tissue, plasma lipoproteins, clotting factors & platelets.<sup>16</sup> Blood stasis & thrombophilia are main factors of thrombus development in venous

system and they may also act in occurrence of ischemic sequel in cases of atrial fibrillation. Disproportion of coagulation system may happen in peri-operative condition or in severe illness, which may be secondary to several factors leading to either thrombosis or bleeding.<sup>17</sup>

## CONCLUSION

Homocysteine level was found to be frequently elevated in patients with ischemic stroke. The role of increased tHcy levels in patients with ischemic stroke should be further evaluated in prospective studies.

## LIMITATIONS

There were no significant limitations.

## SUGGESTIONS / RECOMMENDATIONS

In future, we will screen the stroke patients for homocysteine level and in patients with raised levels will be managed with better management protocol in order to prevent complications of raised homocysteine level along with stroke. But we further recommend to conduct further studies like cohort or case control studies to find the association of raised homocysteine levels with ischemic stroke and morbidity and mortality in these cases.

## CONFLICT OF INTEREST / DISCLOSURE

None.

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## REFERENCES

1. Currie D. Major causes of disability, death shift around the globe: Chronic diseases now taking the lead. *The Nation's Health* 2013;43(1):1-22.
2. American Heart Association. New statistical update looks at worldwide heart, stroke health. DALLAS2014 [cited 2017]; Available from: <http://newsroom.heart.org/news/new-statistical-update-looks-at-worldwide-heart-stroke-health>.
3. Jauch EC, Saver JL, Adams HP, Bruno A, Demaerschalk BM, Khatri P, et al. Guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2013;44(3):870-947.
4. Goldstein LB. Modern medical management of acute ischemic stroke. *Methodist DeBakey Cardiovasc J*. 2014;10(2):99-104.
5. Ashjazadeh N, Fathi M, Shariat A. Evaluation of Homocysteine Level as a Risk Factor among Patients with Ischemic Stroke and Its Subtypes. *Iran J Med Sci*. 2013;38(3):233-9.
6. Esteghamati A, Hafezi-Nejad N, Zandieh A, Sheikhabahaei S, Ebadi M, Nakhjavani M. Homocysteine and metabolic syndrome: from clustering to additional utility in prediction of coronary heart disease. *J Cardiol*. 2014;64(4):290-6.
7. Dhamija RK, Gaba P, Arora S, Kaintura A, Kumar M, Bhattacharjee J. Homocysteine and lipoprotein (a) correlation in ischemic stroke patients. *J Neurol Sci*. 2009;281(1-2):64-8.
8. Lee M, Hong KS, Chang SC, Saver JL. Efficacy of homocysteine-lowering therapy with folic Acid in stroke prevention: a meta-analysis. *Stroke*. 2010;41(6):1205-12.
9. Friedman HS. Serum homocysteine and stroke in atrial fibrillation. *Annals Int Med*. 2001;134(3):253-4.

10. Cingozbay BY, Yiginer O, Cebeci BS, Kardesoglu E, Demiralp E, Dincturk M. Role of homocysteine for thromboembolic complication in patients with non-valvular atrial fibrillation. *Blood Coagul Fibrinolysis*. 2002;13(7):609-13.
11. Narang AP, Verma I, Kaur S, Narang A, Gupta S, Avasthi G. Homocysteine--risk factor for ischemic stroke? *Indian J Physiol Pharmacol*. 2009;53(1):34-8.
12. Wang W, Gao C, Yu C, Liu S, Hou D, Wang Y, Wang C, Mo L, Wu J. No Association between Elevated Total Homocysteine Levels and Functional Outcome in Elderly Patients with Acute Cerebral Infarction. *Front Aging Neurosci*. 2017;9:70.
13. Fiorentino TV, Prioletta A, Zuo P, Folli F. Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. *Curr Pharm Des*. 2013;19(32):5695-703.
14. Yilmaz N. Relationship between paraoxonase and homocysteine: crossroads of oxidative diseases. *Arch Med Sci*. 2012;8(1):138-53.
15. Ganguly P, Alam SF. Role of homocysteine in the development of cardiovascular disease. *Nutr J*. 2015;14:6.
16. Krishna SM, Dear A, Craig JM, Norman PE, Golledge J. The potential role of homocysteine mediated DNA methylation and associated epigenetic changes in abdominal aortic aneurysm formation. *Atherosclerosis* 2013;228(2):295-305.
17. Palta S, Saroa R, Palta A. Overview of the coagulation system. *Indian J Anaesth*. 2014;58(5):515-23.