



# Raised Homocysteine Level in Cases with Ischemic Stroke

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## ABSTRACT

Stroke remains one of the most devastating of all neurological diseases, often causing death or gross physical impairment or disability. Homocysteine is one of the modifiable risk factor regarding this. **Objectives:** To determine the frequency of raised homocysteine level in patients of ischemic stroke. **Material and methods.** This was a cross sectional study that was conducted at Department of Medicine, Shaikh Zayed Hospital, Rahim yar khan between the period of July 2016 to December 2016 in which 146 cases with age range of 40 to 70 years of both gender suffering from ischemic stroke were included and were assessed for their homocysteine level **Results;** In this study there were 146 cases out of which 76 (52.05%) were males and 70 (47.95%) females. The mean age was  $56.25 \pm 7.67$  years and mean BMI was  $29.52 \pm 3.42$ . There were 40 (27.40%) cases with DM, 48 (32.88%) hypertensive, 46 (31.51%) had history of smoking while 18 (12.33%) had family history of ischemic stroke. Raised homocysteine level was seen in 58 (33.70%) cases. Raised homocysteine level was more seen in females where it was seen in 32 (45.71%) out of 70 females as compared to 26 (34.21%) out of 76 males with p values of 0.32. This raised level was also seen maximum in age groups of 60 to 70 years affecting 28 (45.14%) out of 62 cases ( $p=0.43$ ). There was no significant association with any of the risk factors with raised homocysteine level. **Conclusion;** Ischemic stroke is a fatal condition. Raised homocysteine level is seen in every 3<sup>rd</sup> cases of ischemic stroke. Hypertension and family history of ischemic stroke has almost significant association with it.

**Key words;** Stroke, homocysteine

## INTRODUCTION

Stroke remains one of the most devastating of all neurological diseases, often causing death or gross physical impairment or disability. Worldwide, Asia, Russia and Eastern Europe experience the highest rates of mortality and disability and loss of quality of life because of stroke.<sup>1-2</sup>

Atherosclerosis, diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), peripheral arterial diseases are the known risk factors for ischemic stroke. But they are unavoidable and non-modifiable risk factors. It is seen that a good number of cases, these well studied risk factors are even absent too.<sup>3</sup> This opens the horizon to look for new or undiscovered and if possible, the modifiable risk factors associated with

stroke. Homocysteine (Hcy) excess is one of those risk factors, which are modifiable and recently work is going on globally to look for its importance and their role in ischemic stroke.

The raised level of homocysteine occurs due to deviation in the metabolism of Methionine, which is an essential amino acid; leading to hyper coagulable state which cause clotting in blood vessels and lead to ischemic infarcts in brain. It is affected by many factors like age, vitamin B6, B12, Folic acid and intake of certain drugs like steroids and cyclosporine.

Han L et al revealed that the raised levels of homocysteine were not only directly associated with increased risk of stroke but also with the severity of the ischemic stroke and folic acid was found useful for its prevention.<sup>4</sup> According to a study by Ashjazed N et al carried on 171 cases of ischemic

stroke as compared to 82 matched controls, the homocysteine level was found significantly raised in cases with ischemic stroke as compared to controls. 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) ( $P=0.013$ )<sup>5</sup>

According to a study by Sadiq M et al it was seen that raised levels of homocysteine was seen in 58.3% of cases in their study at Karachi.<sup>6</sup> Another study from Bangladesh, done by Rehman et al on 36 patients showed that raised homocysteine levels were seen in 75% of the cases.<sup>7</sup>

## Objective

The objective of this study was to determine the frequency of raised homocysteine level in patients of ischemic stroke in people of Rahim Yar Khan.

## MATERIALS AND METHODS

This was a cross sectional study that was conducted at Department of Medicine, Shaikh Zayed Hospital, Rahim yar khan between the period of July 2016 to December 2016 in which 146 cases of ischemic stroke were included with following inclusion and exclusion criteria.

### Inclusion criteria.

- Gender: both male and female
- Age: 40 – 70 years
- All the patient with ischemic stroke (as per operational definition) presenting within 1 week of the symptoms.

### Exclusion criteria

- Patients with hemorrhagic stroke (hyperdense area on CT brain plain in at least 3 slices)
- Patients with any history of prior stroke in life time.
- Patients taking drugs like multivitamin/steroids/cyclosporine within last two weeks

### Hemorrhagic Stroke

The patients were labeled as having hemorrhagic stroke, when he or she had a history of severe headache and sudden loss of movement in

one or more than one parts of the body. The diagnosis was confirmed on CT scan brain (hyper dense area in the brain in at least 3 slices).

### Hyperlipidemia

Hyperlipidemia was labeled 'yes' when there was any of the following lipid values observed:

1. High serum LDL-C levels:  $>100\text{mg/dl}$
2. Hypertriglyceridemia = serum triglycerides level:  $>150\text{mg/dl}$
3. Hypercholesterolemia= Cholesterol level  $>200\text{mg/dL}$
4. Low HDL:  $<40\text{mg/dL}$

### Statistical Analysis

In this cross sectional study, all the collected data were entered into SPSS version 21 and analyzed. The qualitative data like sex, DM, HTN, Smoking, family history of ischemic stroke, raised level of homocysteine (yes/no) were assessed as frequency and percentages. Quantitative data like age, weight, height, BMI, homocysteine level ( $\mu\text{mol/L}$ ) and duration of symptoms (days) were assessed as means and standard deviations. Post stratification chi square test was applied and p value  $\leq 0.05$  was considered as significant.

## RESULTS

In this study there were 146 cases out of which 76 (52.05%) were males and 70 (47.95%) females. The mean age was  $56.25 \pm 7.67$  years and mean BMI was  $29.52 \pm 3.42$ . There were 40 (27.40%) cases with DM, 48 (32.88%) hypertensive, 46 (31.51%) had history of smoking while 18 (12.33%) had family history of ischemic stroke. Raised homocysteine level was seen in 58 (33.70%) cases. Raised homocysteine level was more seen in females where it was seen in 32 (45.71%) out of 70 females as compared to 26 (34.21%) out of 76 males with p values of 0.32 as shown in Table 1. This raised level was also seen maximum in age groups of 60 to 70 years affecting 28 (45.14%) out of 62 cases followed by 40 to 49 year in 16 (44.44%) out of 36 cases with p values of 0.43 as in table 2. There was no significant association with any of the risk factors with raised homocysteine level as in Table 3.

**Table 1: Raised homocysteine level with respect to gender (n=146).**

Gender	Raised Homocysteine Level		Total
	Yes	No	
Male	26 (34.21%)	50 (65.79%)	76 (100%)
Female	32 (45.71%)	38 (54.29%)	70 (100%)
Total	<b>58 (69.8%)</b>	<b>88 (30.2%)</b>	<b>146 (100%)</b>

Chi square= 1.007, p= 0.32

**Table 2: Raised homocysteine level with respect to age groups (n=146).**

Age group	Raised Homocysteine Level		Total
	Yes	No	
40 to 49	16 (44.44%)	20 (55.56%)	36 (100%)
50 to 59	14 (29.17%)	34 (70.83%)	48 (100%)
60 to 70	28 (45.16%)	34 (54.84%)	62 (100%)
Total	<b>58 (69.8%)</b>	<b>88 (30.2%)</b>	<b>146 (100%)</b>

Chi square= 1.667, p= 0.43

**Table 3: Raised homocysteine level with respect to study variables (n=146).**

		Raised homocystein		P-value
		Yes	No	
<b>DM</b>	Yes	12	28	Chi sq.=1.08 P= 0.29
	No	46	60	
<b>HTN</b>	Yes	18	30	Chi sq. = 0.07 p= 0.78
	No	40	58	
<b>Smoking</b>	Yes	14	32	Chi sq.=1.21 P= 0.27
	No	44	56	
<b>Family h/o Ischemic stroke</b>	Yes	8	10	Chi sq.= 0.09 P= 0.75
	No	50	78	
<b>BMI</b>	< 30	28	46	Chi sq.= 0.11 P=0.73
	> 30	30	42	

## DISCUSSION

Stroke remains one of the most devastating of

all neurological diseases, often causing death or gross physical impairment or disability. Worldwide, Asia, Russia and Eastern Europe experience the highest rates of mortality and disability and loss of quality of life because of stroke.

Raised homocysteine level was seen in 58 (33.70%) cases. Similar was seen by other studies as well.<sup>8-10</sup> The mechanism behind this ischemic stroke is that it increases the tendency of the blood to clot. The above mentioned studies have also build up the association that raised homocysteine level increases the likelihood of developing stroke not only in the smaller vessels but also with the larger ones.<sup>8-10</sup> Even the studies have shown this raised level in as high as 75% of the cases. The reason of such higher number in contrast to our study is unknown. The mortality was not assessed in this study but a study from China has seen for this association. They have noted that elevated tHcy levels during the acute phase of an ischemic stroke significantly increased the mortality chances. In this study majority of the cases were in 2<sup>nd</sup> quartiles of the Hcy level and that study has revealed that the cases with 3<sup>rd</sup> and the 4<sup>th</sup> quartiles had a 1.83-fold or higher increased risk of death after the 48 months of stroke compared with patients in the first quartile. After multivariate analysis, this association remained statistically significant.<sup>12</sup>

Raised homocysteine level was seen in females where it was seen in 32 (45.71%) out of 70 females as compared to 26 (34.21%) out of 76 males; though this difference was not statistically significant with p values of 0.32. A study by Hung et al showed that resistant hypertension was associated with a higher risk of IS, especially in women and elderly patients.<sup>13</sup> The Framingham Heart Study also suggested overall higher lifetime stroke susceptibility in women. Estrogen and estrogen-progestogen therapy can reduce homocysteine levels in menopausal women. Another study suggested that higher levels of estrogen-homocysteine conjugates could lead to a lowering of homocysteine-induced cardiovascular disease (CVD) risk. Here we observed that elderly women tended to have higher tHcy levels, perhaps because of the lower estrogen levels in older women.<sup>14-16</sup>

This raised level was also seen maximum in age groups of 60 to 70 years affecting 28 (45.14%)

out of 62 cases followed by 40 to 49 year in 16 (44.44%) out of 36 cases. This difference was also not found significant with p values of 0.43. This was also observed by many studies.<sup>17</sup> It can be explained by many ways. The higher age was with this increased tendency was explained in females due to hormonal changes. The other factors can be multiple nutritional factor deficiencies like vitamin and antioxidant which is decreased in older age groups to either poor intake or development of comorbidities like GI problems, malignancies etc. that can also either enhance their consumption or decrease their absorption. Contrary to all this, on the other hand the other group which was found higher in this study was relatively young group with age 40 to 49 years. The reason for higher age groups in relatively young age group can be due to genetic factors that were also observed by other studies. However they also did not found significant association.<sup>18-19</sup>

In this study the ischemic stroke was seen in 18 out of 30 cases with a near significant p value of 0.07. This was also seen by other studies that found in higher number.<sup>13-14</sup> Moreover, Yan et al reported that women with mild hypertension had a higher risk of stroke than men and showed that a 10 mm Hg increase in SBP was associated with a 38% increased risk of stroke in women. The other mechanisms involved include the history of pre-existing atherosclerosis, which is also an outcome of DM and HTN. Conflicting results have been found regarding association between homocysteine levels and diabetes mellitus.<sup>20</sup>

The cases with family history of ischemic stroke were found in 8 out of 18 cases with p value of 0.09. This higher number can be explained by the presence of genetic factors. Multiple genetic mutations have been proposed to support this theory with higher Hcy levels than those without pre-existing atherosclerosis. It seems that there is an association between economic prosperity and the risk of stroke. Higher prevalence of Hcy in many developing countries could indicate the role of inadequate intake of vitamins and antioxidants in the multi-factorial causes of stroke. The effect of genetic factors on hyperhomocysteinemia is also important. In fact, these factors may confound the results of epidemiological studies and may render

the results statistically unstable.<sup>21-23</sup>

There were few limitations to this study. As this study did not check for the type of vessel involved in development of stroke and it also did not check for the association of raised level with the severity of the stroke.

## CONCLUSION

Ischemic stroke is a fatal condition. Raised homocysteine level is seen in every 3<sup>rd</sup> cases of ischemic stroke. Hypertension and family history of ischemic stroke has almost significant association with it.

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