SERUM HOMOCYSTEINE LEVELS IN CEREBROVASCULAR ACCIDENTS

Shoukath Abdul Raheem¹

HOW TO CITE THIS ARTICLE:

Shoukath Abdul Raheem "Serum Homocysteine Levels in Cerebrovascular Accidents". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 01, January 06; Page: 192-199

ABSTRACT: AIMS AND OBJECTIVES: To study serum homocysteine levels in cerebrovascular accidents as risk factor for stroke and compare its level in normal subjects. **MATERIALS AND METHODS:** All 50 patients were subjected to history, physical examination, underwent CT Brain and serum homocysteine levels and 50 normal subjects were selected and their serum homocysteine levels were estimated. **OBSERVATIONS AND RESULTS:** Among 50 patients, 43 patients were having infarct in CT BRAIN and their mean homocysteine level was 26.30(+13.80), hemorrhage in 3 patients with mean homocysteine level of 39.97 (+ 14.60), 4 patients showed normal CT with serum homocysteine level 11.39(+6.450). Normal subjects had mean serum homocysteine levels of 9.31. **SUMMARY AND CONCLUSION:** In conclusion the present study revealed that hyper homocysteinemia appears to be an important risk factor for cerebrovascular accidents. It is therefore important to use serum homocysteine level as an important tool to investigate all cases of cerebrovascular accidents and also in those who are at risk of developing stroke. **KEY WORDS:** Homocysteine, stroke, cerebrovascular accident.

INTRODUCTION: Stroke is a common worldwide health problem. It is a major cause of morbidity, mortality and disability in developed countries. After coronary heart disease and all cancers, stroke is the third common cause of death in the world, causing about 4 million deaths in 1990 and three quarters of them in developing countries.¹⁻⁴.

Once the diagnosis of stroke is made, a brain imaging study is necessary to determine cause of stroke is ischemia or hemorrhage. About 85% of all first ever strokes are ischemic, 10% are due to primary intracerebral hemorrhage and about 5% are due to subarachnoid hemorrhage. Within Ischemic stroke, 25% are caused by large artery disease, 25% by small vessel disease, 20% by cardiac embolism, and 05% by other rare causes.^{3,4}.

There are many risk factors for stroke including age, sex, and family history of stroke, hypertension, smoking, diabetes, obesity, hyperlipidemia and atrial fibrillation. Many studies indicate a plethora of conventional risk factors for stroke^{4,5}. Nevertheless, cerebrovascular events do occur sometimes in the individuals without any of the previously mentioned risk factors. As a consequence, it is very likely that there are other risk factors.

Hyperhomocysteinemia is one of independent preventable risk factors for recurrent stroke. Hyperhomocysteinemia, defined as an elevated plasma total homocysteine concentration (10 $\mu\text{M}/\text{dl}$); is one such factor⁶. Hyperhomocysteinemia has also been associated with myocardial infarction, Alzheimer's disease and vascular dementia. Hyperhomocysteinemia is common and is the main prothrombotic factor associated with cerebrovascular accident. Hyperhomocysteinemia is an independent risk factor for arterial dysfunction in healthy middle aged adults.

Hyperhomocysteinemia causes increased arterial blood pressure thereby increasing the risk of cerebrovascular accidents. Elevated plasma homocysteine has also been shown to induce oxidative injury to vascular endothelial cells and cause impairment of the endothelial production of

nitric oxide, a strong vascular relaxing factor. Other proposed mechanisms include enhancement of platelet adhesion to endothelial cells, promotion of the growth of vascular smooth muscle cells and association of increased homocysteine with higher levels of prothrombotic factors such as β -thromboglobulin, tissue plasminogen activator and factor VIIc^{2,6}.

Homocysteine is an amino acid in the blood. It is not obtained from the diet and is biosynthesized from methionine via multi step process. Plasma homocysteine levels are strongly influenced by diet, as well as by genetic factors. The dietary components with the greatest effects are folic acid and vitamins B6 and B12. Folic acid and other B vitamins help break down homocysteine in the body. Several studies have found that higher blood levels of B vitamins are related, at least partly, to lower concentrations of homocysteine. Other recent evidence shows that low blood levels of folic acid are linked with a higher risk of fatal coronary heart disease and stroke⁶.

Several clinical trials are under way to test whether lowering homocysteine will reduce coronary heart disease risk. Recent data show that the institution of folate fortification of foods has reduced the average level of homocysteine in the United States population. Recent findings suggest that laboratory testing for plasma homocysteine levels can improve the assessment of risk. It may be particularly useful in patients with a personal or family history of cardiovascular disease, but in whom the well-established risk factors (smoking, high blood cholesterol, high blood pressure) do not exist⁵.

Patients at high risk should be strongly advised to be sure to get enough folic acid and vitamins as there is evidence of benefit of lowering homocysteine by B6 and B12 in the diet⁵. Foods high in folic acid include green leafy vegetables and grain products fortified with folic acid. A physician taking any type of nutritional approach to reducing risk should consider a person's overall risk factor profile and adjust the diet accordingly. The reason for the decline in the incidence of major stroke in recent years are unclear, may be due to the treatment of risk factors such as hypertension and elevated cholesterol. It has been estimated that full implementation of currently available preventive strategy could reduce stroke incidence by as much as 50 - 80 %.

OBJECTIVES: To study serum homocysteine levels in cerebrovascular accidents as a risk factor for stroke and compare its level in normal subjects.

METHODS AND MATERIAL: All patients of cerebrovascular accidents admitted to Basaveshwara Teaching and General Hospital, Gulbarga over a period of 2 years. 50 controls were selected after matching with age and sex.

NORMAL LEVELS OF HOMOCYSTEINE: Adult male: 06-15 $\mu\text{mol/l}$, Adult female: 03-12 $\mu\text{mol/l}$, Elderly >65 years: 15-20 $\mu\text{mol/l}$, inclusion criteria is patients with neurological deficit suspected cerebrovascular accident, exclusion criteria neurological deficit other than cerebrovascular accident.

ORIGINAL ARTICLE

Age in yrs	Male		Female		Total	
	No of patients	percentage	No of patients	percentage	No of patients	Percentage
<50	06	19.35	00	00	06	12
50-60	11	35.48	01	5.2	12	24
60-70	04	12.90	13	68.42	17	34
70-80	08	25.80	03	15.78	11	22
80&above	02	6.45	02	10.52	04	08
TOTAL	31	100	19	100	50	100
Mean±SD	58.8±14.06		66.98±8.15		62.12±12.41	

Age and sex wise distribution of patients

CT wise	No of patients	percentage	Homocysteine levels Mean±SD
Infarct	43	86	26.30±13.82
Haemorrhage	03	03	39.97±14.60
Normal	04	08	11.39±6.45
Total	50	100	25.5±14.21

Comparison of serum homocysteine level with ct finding

Mean serum homocysteine levels were higher in patients with infarct than in patients with normal CT finding. The difference was statistically highly significant ($p < 0.01$).

Mean serum homocysteine levels were higher in patients with hemorrhage than in patients with normal CT finding. The difference was statistically significant ($p < 0.05$).

Mean serum homocysteine levels were higher in patients with hemorrhage and infarct taken together than in patients with normal CT finding. The difference was statistically significant ($p < 0.05$).

Habits	No of patients	Percentage	Homocysteine LevelMean±SD	t-test value and significance
Smoker	26	52	30.21±14.01	t=2.15p<0.05 significant
Non smoker	24	48	21.22±12.24	
Total	50	100	25.50±14.21	

Comparison of serum homocysteine level with smoking habit

Mean serum homocysteine levels were higher in smokers than non-smokers. The difference was statistically significant ($p < 0.05$).

ORIGINAL ARTICLE

Blood pressure	No of patients	percentage	Homocysteine level mean± sd	t-test value p-value significant
Hypertensive	33	66	30.17±14.2	t=2.78, p<0.05 significant.
Normotensive	17	34	18.96±11.00	
Total	50	100	25.50±14.21	
Comparison of serum homocysteine level with blood pressure				

Mean serum homocysteine levels were higher in hypertensive patients than in normotensive patients. The difference was statistically significant (p<0.05).

Stroke	No of patients	Percentage	Homocysteine level Mean±SD	p-value and significant
Recurrentstroke	14	28	21.74±11.45	T=1.12, p>0.05 Not significant
New onset stroke	36	72	26.75±14.38	
Total	50	100	25.50±14.21	
Comparison of serum homocysteine level with stroke recurrence				

Mean and Standard deviation of serum homocysteine levels were 21.74±11.45 in patients with recurrent stroke and 26.75±14.38 in new onset stroke group. The difference was statistically not significant (p >0.05).

Fasting lipid profile	Number of patient	Percentage	Homocysteine level Mean±SD	P-value and significant
Normal	19	38	26.93±17.48	t=0.33, p>0.05 not significant
Dyslipidemia	31	62	24.95±14.19	
Total	50	100	25.50±14.21	
Comparison of serum homocysteine level with fasting lipid profile				

Mean and Standard deviation of serum homocysteine levels were 26.93±17.48 in patients with normal fasting lipid profile and 24.95±14.19 in patients with dyslipidemia. The difference was statistically not significant (p >0.05).

SL.NO	LEVELS OF HOMOCYSTEINE (μmol/l)	AGE	SEX
1	6.12	53	Female
2	6.55	50	Female
3	12.34	43	Male
4	6.99	44	Male
5	7.87	68	Female
6	6.55	60	Female
7	7.45	54	Male
8	9.87	51	Female
9	7.77	54	Female

ORIGINAL ARTICLE

10	7.56	56	Male
11	8.78	58	Female
12	8.76	55	Female
13	9.70	53	Female
14	9.98	50	Male
15	8.87	49	Male
16	7.88	67	Male
17	11.67	68	Female
18	6.54	52	Female
19	7.98	66	Female
20	6.98	54	Male
21	6.53	54	Male
22	6.78	56	Female
23	7.90	48	Female
24	8.99	65	Female
25	8.79	70	Male
26	9.76	73	Male
27	9.78	70	Male
28	10.03	49	Female
29	7.88	64	Female
30	9.56	62	Female
31	6.88	57	Female
32	7.44	55	Female
33	7.89	51	Male
34	9.00	82	Female
35	12.45	60	Male
36	12.12	83	Male
37	14.46	52	Male
38	13.24	84	Male
39	14.98	55	Male
40	13.56	53	Male
41	13.67	81	Male
42	13.00	76	Male
43	12.87	71	Male
44	12.12	70	Male
45	12.76	65	Male
46	11.56	64	Female
47	9.02	62	Female
48	8.99	51	Male
49	8.87	44	Male
50	8.90	50	Female

CONTROLS SERUM HOMOCYSTEINE LEVELS OF 50 CONTROLS.

DISCUSSION: Many studies have showed that increased homocysteine represents an independent risk factor for coronary, cerebrovascular and peripheral arterial disease. Various risk factors for cerebrovascular accidents like age, sex, hypertension, and lifestyle were studied and analyzed in relation to serum homocysteine levels. Hyperhomocysteinemia is one of the newly recognized factors that increase the risk of vascular disease.

Mechanisms by which hyperhomocysteinemia increases risk of cerebrovascular accidents are not clear, but several possible mechanisms have been proposed. Hyperhomocysteinemia is associated with premature atherosclerosis. Experimental studies both in vivo and in vitro shows that homocysteine causes endothelial injury and cell detachment. Hence these data suggest that homocysteine might contribute to cerebrovascular disease in patients as an additive risk factor. Measurement of homocysteine may become the integral part of workup of stroke patients in future.

In this study of 50 patients, 25 (50%) patients were <65 years of age and 25 (50%) were ≥65 years of age. Mean serum homocysteine levels were higher in patients less than 65 years of age (26.19) than in patients more than or equal to 65 years of age (24.8). However, the difference was statistically not significant ($p > 0.05$). Our findings were consistent with study of Narang et al, Modi et al and Nigel et al. However, according to findings of Longo et al and Zongte et al increase in the serum homocysteine levels were observed with increasing age.

In this study of 50 patients presenting with neurological deficits due to cerebrovascular accidents, 34 male patients with the mean age of 58.8 years and 19 female patients with the mean age of 66.98 years were studied. The present study showed that according to age and sex wise distribution of patients male patients were of younger age as compared to female patients. The difference was statistically significant ($p < 0.05$). Our study consisted of 26 (52%) smokers and 24 (48%) non-smokers. Mean serum homocysteine levels in smokers was higher (30.21) than non-smokers (21.22). The difference was statistically significant ($p < 0.05$). Our results were similar to findings of Modi et al⁶, Nygard et al and Welch et al. However Roudbari et al reported no significant relationship between smoking and serum homocysteine levels. Perry et al found no evidence of an interaction with smoking.

In our study, 33 (66%) patients were hypertensive and 17 (34%) were normotensives. Mean serum homocysteine levels were higher in hypertensive patients (30.17) than normotensive patients (18.96). The difference was statistically significant ($p < 0.05$). Our results were similar to findings of Narang et al, Modi et al, Graham et al, Olusegun et al, Nigel et al, Nygard et al, Perry et al and Manilow et al. However Kittner et al did not find definite evidence of an increased homocysteine in hypertensive patients.

Our study consisted of 18 (28%) patients with stroke recurrence and 36 (72%) patients with new onset stroke (first time stroke). Mean and Standard deviation of serum homocysteine levels were 21.74 ± 11.45 in stroke recurrence group and 26.75 ± 14.38 in new onset stroke group. The difference was statistically not significant ($p > 0.05$). However Boysen et al and Del Ser et al reported significantly higher serum homocysteine levels in recurrent stroke patients. Brattstrom et al and Lindgren et al found no difference in homocysteine between patients who previously had cerebral infarcts and hemorrhage.

In our study, 19 (38%) patients were having normal fasting lipid profile and 29 (62%) patients were having dyslipidemia. Mean and Standard deviation of serum homocysteine levels were 26.93 ± 17.48 in patients with normal fasting lipid profile and 24.95 ± 14.19 in patients with

dyslipidemia. The difference was statistically not significant ($p > 0.05$). Our findings were similar to study of Narang et al and Modi et al.

In our study, 43 (86%) patients were having infarct, 3 (6%) patients were having hemorrhage and 4 (8%) patients were having normal CT finding. Mean homocysteine levels were higher with infarct (26.30) and hemorrhage (39.97) than in patients with normal CT finding (11.39). The difference was statistically significant with both infarct ($p < 0.01$) and hemorrhage ($p < 0.05$). Our findings were consistent with study of Datta et al and Boysen et al where serum homocysteine levels were significantly raised in infarcts when compared to hemorrhage.

Clarke R et al, Olsegun et al, Osunkalu et al, Kittner et al, Bruce et al, Perry et al and Zongte et al concluded hyperhomocysteinemia as an independent predictor of stroke risk (both infarct and hemorrhage).

All the patients were subjected to thorough history, clinical examination and investigations including fasting lipid profile, CT scan brain and serum homocysteine. Our main observation was that serum homocysteine levels were elevated in cerebrovascular accident patients significantly, both in cases of infarct and hemorrhage. Further serum homocysteine levels were higher in patients with sedentary lifestyle, hypertension and smoking.

Serum homocysteine did not show any relation with age, sex, diabetes mellitus and stroke recurrence. People at risk for cerebrovascular diseases such as hypertension, smoking and sedentary lifestyle should be screened for hyperhomocysteinemia. Normal subjects had mean homocysteine levels of 9.31 ± 5.6 .

SUMMARY: All the patients were subjected to thorough history, clinical examination and investigations including fasting lipid profile, CT scan brain and serum homocysteine.

Our main observation was that serum homocysteine levels were elevated in cerebrovascular accident patients significantly, both in cases of infarct and hemorrhage. Further serum homocysteine levels were higher in patients with sedentary lifestyle, hypertension and smoking.

Serum homocysteine did not show any relation with age, sex, diabetes mellitus and stroke recurrence.

People at risk for cerebrovascular diseases such as hypertension, smoking and sedentary lifestyle should be screened for hyperhomocysteinemia.

Serum homocysteine did not show any variation with respect age, sex and mean value is 9.31 ± 5.6 .

CONCLUSION: In conclusion the present study revealed that hyperhomocysteinemia appears to be an important risk factor for cerebrovascular accidents. It is therefore important to use serum homocysteine level as an important tool to investigate all cases of cerebrovascular accidents and also in those who are at risk of developing stroke

BIBLIOGRAPHY:

1. Datta S, Pal SK, Mazumdar H et al. Homocysteine and cerebrovascular accidents. J Indian Med Assoc 2009 June; 107(6):345-6.
2. Narang APS, Indu Verma, Satinder Kaur et al. Homocysteine- Risk factor for ischemic stroke? Indian J Physiol Pharmacol 2009; 53(1):34-38.

ORIGINAL ARTICLE

3. Susan Standing. Gray's anatomy -The anatomical basis of clinical practice. 40thed, New York: Elsevier Churchill Livingstone; 2008. p.227, 253.
4. Peter Rothwell. Cerebrovascular diseases. In: Michael Donarghy, editor. Brain's diseases of the nervous system. 12thed, New York: Oxford University Press: 2009. p. 1003-16.
5. Longo DL, Fauci AS, Kasper DL et al, editors. Harrison's principles of internal medicine. 18thed. New York: Mc Grath Hill; 2011.
6. Modi M, Prabhakar S, Majumdar S et al. Hyperhomocysteinemia as a risk factor for ischemic stroke: an Indian scenario. Neurology India 2005.

AUTHORS:

1. Shoukath Abdul Raheem

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Medicine, Affiliated to MR Medical College, Gulbarga.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr.Shoukath Abdul Raheem,
H. No. 6-14, A, Mijgori Road,
Mominpura, Gulbarga – 585101.
Email- shoukathabdulraheem@gmail.com

Date of Submission: 28/11/2013.
Date of Peer Review: 29/11/2013.
Date of Acceptance: 17/12/2013.
Date of Publishing: 03/01/2014