

Correlation between Serum Homocysteine and Cerebral Ischemic Stroke in an Urban South Indian Population

T. B. Umadevi¹, S. Chandrasekar²

¹Associate Professor, Department of Internal Medicine, Government Thiruvarur Medical College, Thiruvarur, Tamil Nadu, India

²Associate Professor, Department of Internal Medicine, Government Thiruvarur Medical College, Thiruvarur, Tamil Nadu, India

Abstract: *Ischemic stroke is one of the common diseases found in medical wards, and is one of the common causes of morbidity and mortality worldwide. There are many causes of ischemic stroke and hyperhomocysteinemia is one of the documented causes. Atherogenic nature of homocysteine plays an important role in the development of ischemic stroke. The aim of this study is to correlate homocysteine and cerebral ischemic stroke.*

Keywords: Homocysteine, Ischemic stroke, Hyperhomocysteinemia

1. Introduction

Cerebrovascular accident has become a main health problem and is the most common cause of morbidity and mortality [1]. Stroke is mainly classified into ischemic and hemorrhagic [2]. The commonest etiology for ischemic stroke includes atherosclerosis and cardiogenic thromboembolism [2]. Other risk factors are hypertension, diabetes, cigarette smoking and obesity which are modifiable [2] and biochemical markers like dyslipidemia [3], hypercholesterolemia [4] and hyperhomocysteinemia [5]. Hyperhomocysteinemia has been recently recognized as an easily modifiable risk factor for cerebrovascular accident [6].

Homocysteine is synthesized in our body from methionine in a multistep process [7]. Hyperhomocysteinemia has been found to be an independent risk factor for ischemic stroke. Serum homocysteine (S. HOM) levels more than 15 $\mu\text{mol/L}$ is considered to be associated with an increased risk of ischemic stroke. Hyperhomocysteinemia creates a proatherogenic and prothrombotic environment in the blood vessels [8]. The main mechanism for this is endothelial cell injury. This initiates the atherosclerotic cascade [8]. Other mechanisms include disruption of the normal clotting mechanisms by inhibition of protein C & antithrombin III and activation of factors 5, 10 and 12. It increases thromboxane A2 synthesis leading to platelet aggregation. It causes smooth muscle proliferation, decreases nitric oxide release and increases production of free radicals. All these factors occurring in the cerebral blood vessels lead to formation of a thrombus in these vessels, leading to ischemic stroke. Patients with hyperhomocysteinemia in ischemic stroke should undergo routine ischemic stroke treatment (tPA/ endoscopic revascularization/ aspirin). Along with that they should receive vitamin supplementation with adequate folic acid and vitamin B12 [9].

2. Aims and Objectives

- To correlate risk factors of ischemic stroke with Homocysteine level
- To correlate the clinical profile of ischemic stroke with Homocysteine level

3. Materials and Methods

3.1 Materials

A prospective observational study was undertaken in The Department of Internal medicine, Government Stanley Medical College and Hospital, Chennai from November 2013 to September 2014.

3.1.1 Patient Selection

Patients with ischemic stroke in medical outpatient department and medical wards.

3.1.2 Sample size

75 patients

3.2 Methodology

Blood samples of patients admitted with symptoms suggestive of ischemic stroke with CT brain evidence were taken for serum homocysteine measurements.

3.2.1 Exclusion Criteria

Hemorrhagic stroke, patients on folic acid supplements, patients on anti-epileptics/ oral contraceptive pills/ drugs causing hyperhomocysteinemia, chronic kidney disease, pre-existing coronary artery disease.

3.2.2 Statistical Analysis

Data was analyzed with spss (statistical package for the social sciences) software version 16.0 for windows. All continuous data were expressed as mean and SD and analyzed using student's t-test. Categorical data were

expressed as number (percentage) and analyzed by chi square or fisher's exact test. Pearson's correlation coefficient and linear regression analysis were undertaken to establish correlation and regression among variables. p-value of < 0.05 was considered as statistically significant.

3.2.3 Study Subjects

All the patients who fulfilled the inclusion criteria were included in this study. They were subjected to detailed history taking, complete physical examination and relevant laboratory investigations as per the proforma, exclusively designed for the study.

4. Results and Discussion

4.1 Risk factors – Non-modifiable

4.1.1 Age

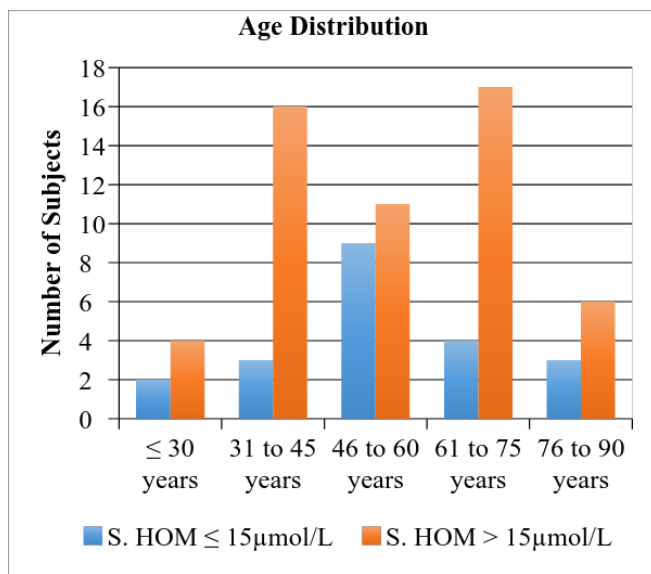


Figure 1: Correlation of serum homocysteine levels with age

Table 1: Statistical correlation of serum homocysteine levels with age

Age Distribution	S. HOM ≤ 15 μmol/L	S. HOM > 15 μmol/L
N	21	54
Mean	55.66667	55.87037
SD	14.51666	16.75128
p-value Unpaired t- test	0.9586	

By conventional criteria, the association between the serum homocysteine groups and age is considered not to be statistically significant since $p > 0.05$.

4.1.2 Gender

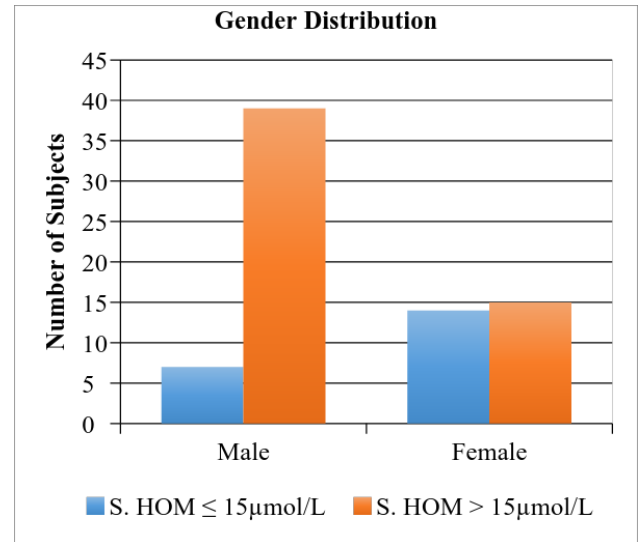


Figure 2: Correlation of serum homocysteine levels with gender

Table 2: Correlation of serum homocysteine levels with gender

Gender Distribution	S. HOM ≤ 15 μmol/L	%	S. HOM > 15 μmol/L	%
Male	7	33.33	39	72.22
Female	14	66.67	15	27.78
Total	21	100	54	100
Chi-square Statistic	9.64			
Degrees of freedom	1			
p-value Chi-square Test	.200			

By conventional criteria, the association between the serum homocysteine groups and gender is considered not to be statistically significant since $p > 0.05$.

Since age and gender is not statistically significant, it means that there is no difference between the groups.

4.2 Risk factors - Modifiable

4.2.1 Smoking

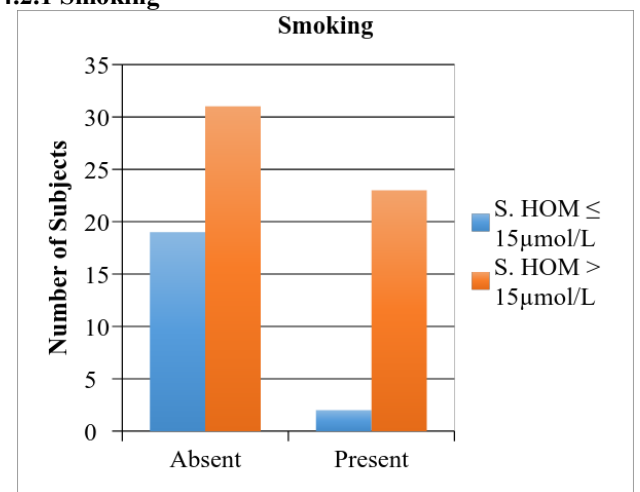


Figure 3: Correlation of serum homocysteine levels with smoking

Table 3: Correlation of serum homocysteine levels with smoking

Smoking	S. HOM $\leq 15\mu\text{mol/L}$		S. HOM $> 15\mu\text{mol/L}$	
	Absent	19	90.48%	31
Present	2	9.52%	23	42.59%
Total	21	100%	54	100%
Chi-square Statistic	9.41			
Degrees of freedom	1			
p-value Chi-square Test	0.002			

By conventional criteria, the association between the serum homocysteine groups and smoking is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and that difference is significant. In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of smoking is 2 in patients with serum homocysteine levels $\leq 15\mu\text{mol/L}$ and 23 in patients with serum homocysteine levels $> 15\mu\text{mol/L}$ with a p-value of 0.002 according to Chi-Square test.

4.2.2 Alcoholism

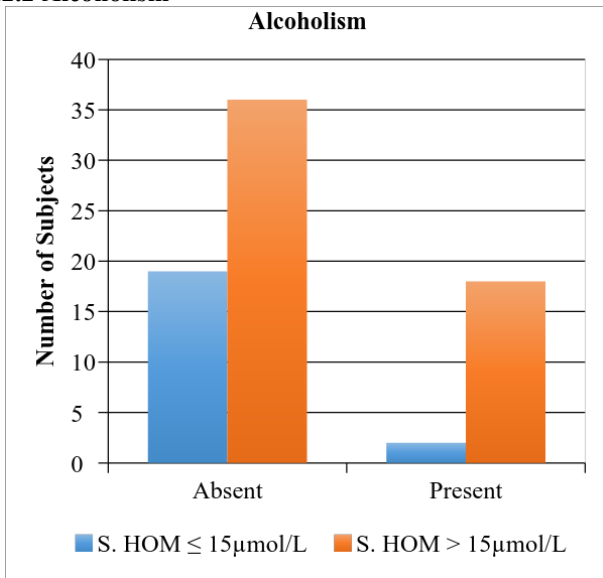


Figure 4: Correlation of serum homocysteine levels with alcoholism

Table 4: Correlation of serum homocysteine levels with alcoholism

Alcoholism	S. HOM $\leq 15\mu\text{mol/L}$		S. HOM $> 15\mu\text{mol/L}$	
	Absent	19	90.48%	36
Present	2	9.52%	18	33.33%
Total	21	100%	54	100%
Chi-square Statistic	4.38			
Degrees of freedom	1			
p-value Chi-square Test	0.036			

By conventional criteria, the association between the serum homocysteine groups and alcoholism is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and that difference is significant. In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of alcoholism is 2 in patients with serum homocysteine levels $\leq 15\mu\text{mol/L}$ and 18 in patients with serum homocysteine levels $> 15\mu\text{mol/L}$ with a p-value of 0.036 according to Chi-Square test.

4.2.3 Hypertension

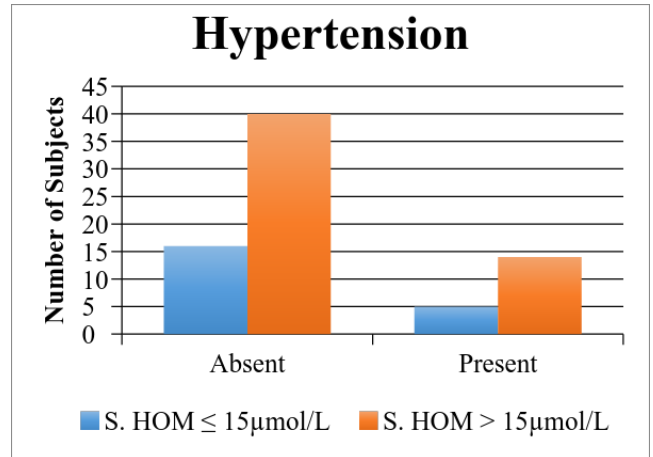


Figure 5: Correlation of serum homocysteine levels with hypertension

Table 5: Correlation of serum homocysteine levels with hypertension

Hypertension	S. HOM $\leq 15\mu\text{mol/L}$		S. HOM $> 15\mu\text{mol/L}$	
	Absent	16	76.19%	40
Present	5	23.81%	14	25.93%
Total	21	100%	54	100%
Chi-square Statistic	0.358			
Degrees of freedom	1			
p-value Chi-square Test	0.850			

By conventional criteria, the association between the serum homocysteine groups and hypertension is considered not to be statistically significant since $p > 0.05$.

4.2.4 Diabetes

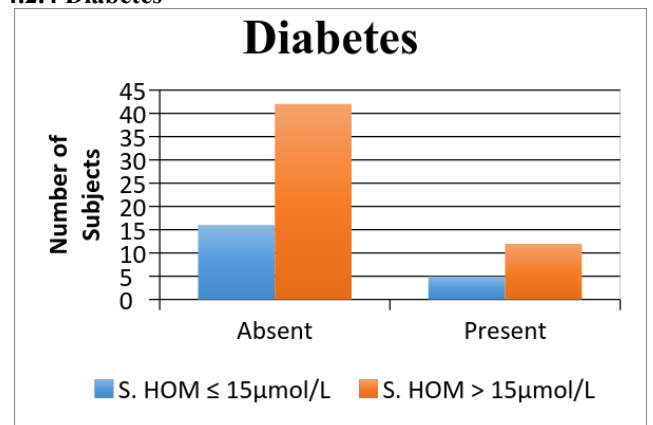


Figure 6: Correlation of serum homocysteine levels with diabetes

Table 6: Correlation of serum homocysteine levels with diabetes

Diabetes	S. HOM $\leq 15\mu\text{mol/L}$		S. HOM $> 15\mu\text{mol/L}$	
	Count	%	Count	%
Absent	16	76.19%	42	77.78%
Present	5	23.81%	12	22.22%
Total	21	100%	54	100%
Chi-square Statistic	0.217			
Degrees of freedom	1			
p-value Chi-square Test	0.883			

By conventional criteria, the association between the serum homocysteine groups and diabetes mellitus is considered not to be statistically significant since $p > 0.05$.

4.2.5 Dyslipidaemia

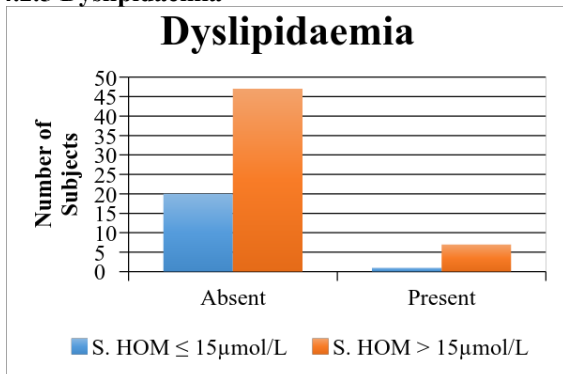


Figure 7: Correlation of serum homocysteine levels with dyslipidaemia

Table 7: Correlation of serum homocysteine levels with dyslipidaemia

Dyslipidaemia	S. HOM $\leq 15\mu\text{mol/L}$		S. HOM $> 15\mu\text{mol/L}$	
	Count	%	Count	%
Absent	20	95.24%	47	87.04%
Present	1	4.76%	7	12.96%
Total	21	100%	54	100%
Chi-square Statistic	1.07			
Degrees of freedom	1			
p-value Chi-square Test	0.302			

By conventional criteria, the association between the serum homocysteine groups and hyperlipidaemia is considered not to be statistically significant since $p > 0.05$.

4.3. Clinical Profile

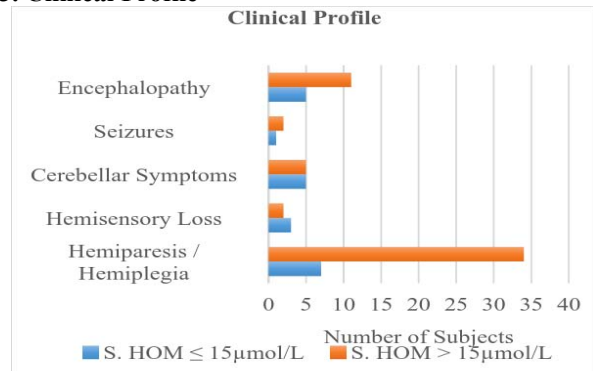


Figure 8: Correlation of serum homocysteine levels with clinical profile

Table 8: Correlation of serum homocysteine levels with clinical profile

Clinical Profile	S.HOM $\leq 15\mu\text{mol/L}$		S.HOM $> 15\mu\text{mol/L}$		P value Chi Square Test
	Count	%	Count	%	
Hemiparesis / Hemiplegia	7	33.33	34	62.96	0.021
Hemi sensory Loss	3	14.29	2	3.70	0.099
Cerebellar Symptoms	5	23.81	5	9.26	0.096
Seizures	1	4.76	2	3.70	0.834
Encephalopathy	5	23.81	11	20.37	0.744
Total	21	100	54	100	

By conventional criteria,

- The association between the serum homocysteine groups and clinical features like hemi sensory loss, cerebellar symptoms, seizures and encephalopathy are considered not to be statistically significant since $p > 0.05$.
- The association between the serum homocysteine groups and hemiparesis/hemiplegia is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and that difference is significant. In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of hemiparesis/hemiplegia is 7 in patients with serum homocysteine levels $\leq 15\mu\text{mol/L}$ and 34 in patients with serum homocysteine levels $> 15\mu\text{mol/L}$ with a p-value of 0.021 according to Chi-Square test.

Clinical Significance

The incidence of hemiparesis/hemiplegia among ischemic stroke patients with serum homocysteine levels $> 15\mu\text{mol/L}$ (82.93%) was significantly higher compared to that in patients with serum homocysteine levels $\leq 15\mu\text{mol/L}$ (17.07%). This difference is true and significant and has not occurred by chance.

4.4. Site of Infarct

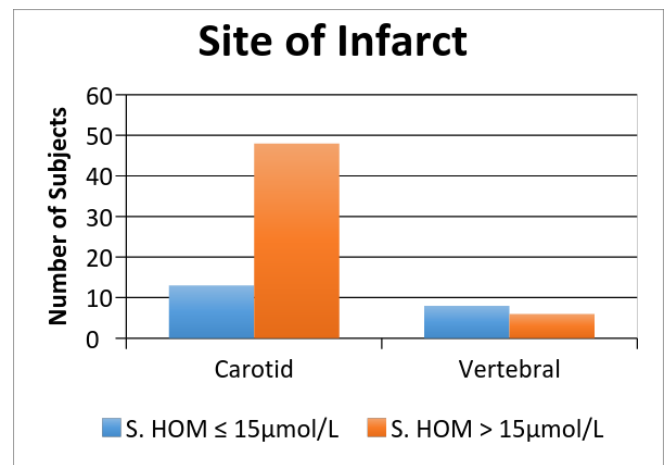


Figure 9: Correlation of serum homocysteine levels with site of infarct

Table 9: Correlation of serum homocysteine levels with site of infarct

Site of Infarct	S. HOM $\leq 15\mu\text{mol/L}$		S. HOM $> 15\mu\text{mol/L}$	
	N	%	N	%
Carotid	13	61.90%	48	88.89%
Vertebral	8	38.10%	6	11.11%
Total	21	100%	54	100%
Chi-square Statistic	7.25			
Degrees of freedom	1			
p-value Chi-square Test	0.007			

By conventional criteria, the association between the serum homocysteine groups and site of infarct is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and that difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the incidence of infarct in carotid artery is 13 in patients with serum homocysteine levels $\leq 15\mu\text{mol/L}$ and 48 in patients with serum homocysteine levels $> 15\mu\text{mol/L}$ with a p-value of 0.007 according to Chi-Square test.

Clinical Significance

The incidence of infarct in carotid artery territory among ischemic stroke patients with serum homocysteine levels $> 15\mu\text{mol/L}$ (89.99%) was significantly higher compared to that in patients with serum homocysteine levels $\leq 15\mu\text{mol/L}$ (61.90%). This difference is true and significant and has not occurred by chance.

4.5. Serum homocysteine:

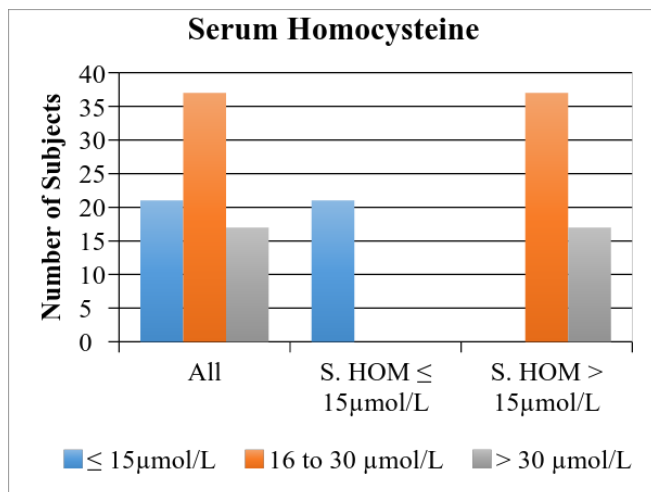


Figure 10: Distribution of serum homocysteine levels among study subjects

Table 10: Distribution of serum homocysteine levels among study subjects

Serum Homocysteine	All		S.HOM $\leq 15\mu\text{mol/L}$		S. HOM $> 15\mu\text{mol/L}$	
	N	%	N	%	N	%
$\leq 15\mu\text{mol/L}$	21	28.00	21	100	0	0.00
16 to $30\mu\text{mol/L}$	37	49.33	0	0.00	37	68.52
$> 30\mu\text{mol/L}$	17	22.67	0	0.00	17	31.48
Total	75	100	21	100	54	100

Table 11: Statistical significance of serum homocysteine levels among study subjects

Serum Homocysteine	All	S. HOM $\leq 15\mu\text{mol/L}$	S. HOM $> 15\mu\text{mol/L}$
N	75	21	54
Mean	24.19	11.99	28.93
SD	12.25	1.71	11.25
p-value Unpaired t test	0.000		

By conventional criteria, the association between the serum homocysteine groups is considered to be statistically significant since $p < 0.05$.

Statistical Significance

This indicates that there is a true difference among the study groups and that difference is significant.

In simple terms, while studying hyperhomocysteinemia in ischemic stroke patients, the average serum homocysteine values in serum homocysteine levels $\leq 15\mu\text{mol/L}$ group is $11.99 \pm 1.71\mu\text{mol/L}$ and in serum homocysteine levels $> 15\mu\text{mol/L}$ group is $28.93 \pm 11.25\mu\text{mol/L}$ with a p-value of 0.000 according to Unpaired t test.

Clinical Significance

The average serum homocysteine values among ischemic stroke patients with serum homocysteine levels $> 15\mu\text{mol/L}$ was 2.41 times more significant than that in patients with serum homocysteine levels $\leq 15\mu\text{mol/L}$ with a difference of $16.94\mu\text{mol/L}$. This difference is true and significant and has not occurred by chance.

5. Conclusion

Hyperhomocysteinemia is closely related to ischemic stroke. It has been recognized as a prothrombotic and proatherosclerotic state and is attributed as one of the causes of ischemic stroke. In our study, the prevalence of hyperhomocysteinemia in patients with ischemic stroke was 54 out of 75 patients, i.e. 72%. This correlates with various Indian studies done elsewhere. It was also found that serum homocysteine level correlated with alcoholism and smoking as p values were significant ($p < 0.05$). The correlation of homocysteine to age, gender, diabetes, hypertension, dyslipidemia at the time of presentation was not statistically significant ($p > 0.05$). The clinical profile of ischemic stroke patients admitted in Government Stanley Hospital, Chennai revealed that the most common presentation during admission is hemiplegia/hemiparesis (41 patients out of 75).

Other presentations in decreasing order of frequency include acute encephalopathy followed by cerebellar symptoms. The site of infarct in anterior circulation strokes involving the carotid artery was found to have a significant statistical correlation with elevated homocysteine levels.

We conclude that hemiparesis/hemiplegia in our study is associated with higher serum homocysteine levels > 15µmol/L in ischemic stroke patients. More studies with similar indices have to be done to confirm the results.

6. Financial Support and Sponsorship

Nil

7. Conflicts of Interest

There are no conflicts of interest.

8. Future Scope

More studies with similar indices have to be done to confirm the results. Previous studies have revealed that hyperhomocysteinemia appears to be an important risk factor for cerebrovascular accidents [10].

References

- [1] Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*. 1997; 349: 1498–1504.
- [2] Itrat A, Ahmed B, Khan M, Muhammad M, Risk factor profiles of South Asians with cerebrovascular disease *Int J Stroke*. 2011 Aug; 6(4):346-8.10.1111/j.1747-4949.2011.00622.x
- [3] Qian Jia, MD, Liping Liu, MD, PhD, Yongjun Wang, Risk Factors and Prevention of Stroke in the Chinese Population: *Journal of Stroke and Cerebrovascular Diseases* Volume 20, Issue 5, September–October 2011, Pages 395–400
- [4] Baidarbhi Chakraborty, Gaurav Vishnoi, Binita Goswami, Lipoprotein (a), Ferritin, and Albumin in Acute Phase Reaction Predicts Severity and Mortality of Acute Ischemic Stroke in North Indian Patients: *Journal of Stroke and Cerebrovascular Diseases* 2012.10.013, 10.1016
- [5] Bertsch T, Mielke O, Höly S, Zimmer W, Casarin W, Homocysteine in cerebrovascular disease: an independent risk factor for subcortical vascular encephalopathy: *Clin Chem Lab Med*. 2001 Aug;39(8):721-4
- [6] Abraham R, John MJ, Calton R, Dhanoa J. Raised serum homocysteine levels in patients of coronary artery disease and the effect of vitamin b12 and folate on its concentration. *Indian Journal of Clinical Biochemistry* 2006; 21(1):95-100.
- [7] Mudd, S. H. et al. Homocysteine and its disulfide derivatives: A suggested consensus terminology. *Arterioscler Thromb Vasc Biol*. 20, 1704–1706 (2002).

- [8] Hanke, Graeme J.; Eikelboom, John W: Homocysteine and stroke: *Current Opinion in Neurology*: February 2001 - Volume 14 - Issue 1 - pg 95-102
- [9] Hankey GJ, Eikelboom JW. Homocysteine and vascular disease. *Lancet*. 1999; 354:407–413.
- [10] Shoukath Abdul Raheem: Serum homocysteine levels in cerebrovascular accidents: *Journal of evolution of medical and dental sciences*: January 2014 – Volume 3 – Issue 1- pg 192-199

Author Profile



T. B. Umadevi is working as Associate Professor, Department of Internal Medicine at Government Thiruvapur Medical College, Thiruvapur, TamilNadu. She has been working in the Department of Internal Medicine for the past 9 years.



S. Chandrasekar is working as Associate Professor, Department of Internal Medicine, Government Thiruvapur Medical College, Thiruvapur, TamilNadu. He has been working in the Department of Internal Medicine for the past 14 years.