



HOMOCYSTEINE: AN INSTIGATING FACTOR FOR ISCHEMIC STROKE

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ABSTRACT

AIM: to find the relationship between serum homocysteine levels and risk of ischemic stroke.**MATERIAL AND METHOD:** A Hospital based observational study was conducted, in which 50 ischemic stroke patients and 30 controls were included. Socio-demographic profile, history, physical and radiological examination, serum homocysteine levels were recorded and analyzed by using descriptive statistical methods.**RESULTS:** Majority of cases and control were male and were in age group of 50-60 years. Homocysteine levels were observed to be significantly ($p=0.0001$) higher among cases (21.69 ± 6.33) compared to controls (11.84 ± 3.88). Serum homocysteine levels are having good sensitivity (80%) and specificity (76.7%) in predicting ischemic stroke.**CONCLUSION:** Serum homocysteine levels are good predictor of ischemic stroke. But, further studies are needed to search for exact causal role of increased homocysteine in ischemic stroke patients with larger sample size.**KEYWORDS :** Homocysteine, Risk Factor, Ischemic Stroke

(World Health Organization [WHO], 1988) definition of stroke is: "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin". Stroke is second most common cause of death in world (Murray & Lopez, 1997). Anand, Chowdury, Singh, Pandav and Kapoor (2001) found that the prevalence of stroke was 203 per 100,000 populations above 20 years (resulting in about 1 million cases) and contributing for 1.2 per cent of the total deaths (approximately 102,000 deaths).

Stroke is divided into ischemic and hemorrhagic types. According to American Stroke Association, 87 % of strokes are classified as ischemic stroke or cerebral infarction (Roger, 2012). Infarcts occur as a result of insufficient or interrupted flow of blood to an area of the brain, typically caused by blockage of an artery (Torbey & Bhardwaj, 2004).

Estimates by (World Health Organization [WHO], 2005) suggest stroke cases to be 80% in low and middle income countries; particularly in India and China. Thus, identification and management of possible risk factors to prevent stroke is an important strategy to reduce human and economic burden of stroke (Warlow, Sudlow, Dennis, Wardlaw & Sandercock, 2003).

Recently, there has been much interest in homocysteine, a sulphur containing amino acid as an important risk factor for vascular diseases including stroke independent of long recognising factors like hyperlipidemia, hypertension, diabetes mellitus and smoking (Pery et al., 1995).

Homocysteine is a sulphur containing amino acid formed during metabolism of methionine, an essential amino acid derived from dietary protein (Cheng, Yang, & Wang, 2009). Hyperhomocysteinemia is defined as a medical condition characterized by an abnormally high level (above $15 \mu\text{mol/L}$) of homocysteine in the blood (Guo, Chi, Xing & Wang, 2009).

Large epidemiological studies have demonstrated positive relationship of hyperhomocysteinemia with coronary artery, peripheral arterial and cerebrovascular diseases (Graham, 1997; Welch, 1998). While others could not establish the same (Peterson, 1998; Toole, 2004).

So, present study was done to estimate serum homocysteine levels in patients with ischemic stroke and to compare these with levels of

homocysteine in controls and to find the relationship, if any, between serum homocysteine levels and risk of ischemic stroke.

METHOD

It was a Hospital based observational study which was conducted in Department of General Medicine in collaboration with the Department of Neurology, Batra Hospital and Medical Research Centre, New Delhi. 50 ischemic stroke inpatients and 30 age and sex matched controls were included in this study.

CRITERIA:

Subjects with first episode of ischemic stroke diagnosed clinically and by imaging studies, presenting within two weeks of event and given their consent were included in study. Whereas subjects having cerebral haemorrhage, venous thrombosis, hypoperfusion or having confounding factors which could raise homocysteine levels like patients taking antiepileptic drugs, L-dopa, folate antagonists like methotrexate, cholestyramine, penicillamine, OCPs, Hormonal replacement therapy or on regular vitamin supplementation mainly vitamin B12 and folate or with renal impairment or ESRD on haemodialysis, malignant disease, cardioembolic disorders were excluded.

Identification data, history, physical and radiological examination of ischemic stroke patients and subjects in control group along with their serum homocysteine levels were recorded in study proforma. Results were analysed and interpreted to see the correlation between serum homocysteine levels in patients with ischemic stroke as compared to controls.

RESULT**Table-1: Age distribution of the cases and controls**

Age in years	Cases (n=50)		Controls (n=30)		p-value ¹
	No.	%	No.	%	
<50	20	40.0	11	36.7	0.50
50-60	23	46.0	17	56.7	
>60	7	14.0	2	6.7	
Mean \pm SD	51.88 \pm 7.46	51.93 \pm 5.67			

¹Chi-square test

Table-1 shows the age distribution of the cases and controls. More than one third of the cases (46%) and controls (56.7) were in the age group 50-60 years.

Table-2: Gender distribution of the cases and controls

Gender	Cases (n=50)		Controls (n=30)		p-value ¹
	No.	%	No.	%	

Male	35	70.0	20	66.7	0.75
Female	15	30.0	10	33.3	

¹Chi-square test

Table-2 shows the gender distribution of the cases and controls. Majority of the cases (70%) and controls (66.7%) were males.

Table-3: Comparison of homocysteine level

Groups	Homocysteine level (μmol/L)	OR (95%CI) ¹
Cases	21.69±6.33	1.42 (1.22-1.64)
Controls	11.84±3.88	1.00 (Ref.)
p-value ¹	0.0001*	

¹Univariate binary logistic regression, OR-Odds ratio, CI-Confidence interval, ²Unpaired t-test, *Significant

Table-3 shows the comparison of homocysteine level between cases and controls. The homocysteine level was observed to be significantly (p=0.0001) higher among the cases (21.69±6.33) compared to controls (11.84±3.88). The univariate logistic regression analysis revealed that the homocysteine level was 1.42 times higher among the cases compared to controls (OR=1.42, 95%CI=1.22-1.64).

Table-4: Sensitivity and specificity of homocysteine in predicting the ischemic stroke (Cutoff value>14.75)

Sensitivity	80.0
Specificity	76.7
Positive predictive value (PPV)	85.1
Negative predictive value (NPV)	69.7
Accuracy	78.8

The receiving operating curve analysis revealed that there was good sensitivity (80%) and specificity (76.7%) of homocysteine cutoff value>14.75 in predicting the cases. The PPV (85.1%) and accuracy (78.8%) was also found to be good.

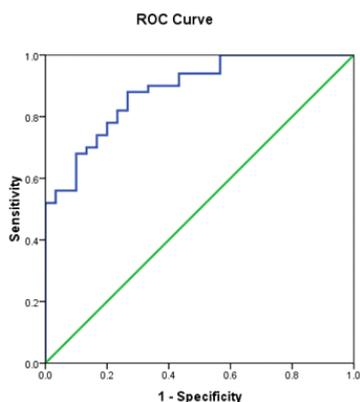


Fig.1: ROC showing sensitivity and specificity of homocysteine in predicting the ischemic stroke (AUC=0.88, 95%CI=0.81-0.96, p=0.03)

DISCUSSION

Stroke is looming as an increasing public health problem, since it is a leading cause of long-term disability among adults in both developed and developing countries. Early detection and control of risk factors is thought to be crucial in reducing the risk of stroke and providing effective care (Uno, Kitazato, Nishi, Itabe & Nagahiro, 2003). A total of 50 patients of ischemic stroke and 30 controls matched for age and sex were enrolled in the study.

Mean age of cases was 51.88±7.46 years. More than one third of the cases (46%) and controls (56.7) were in the age group of 50-60 years. It was comparative with the finding of other studies (Dhamija, 2009; Narang, 2009).

In this study, majority of cases (70%) were male. Other studies also

found male predominance (Narang, 2009; Pniewski, 2003; Tan, 2002).

It was found that homocysteine level was observed to be significantly higher among the cases as compared to controls. Similar results were also found in various studies (Dhamija, 2009; Narang, 2009; Omrani, 2011). This can be due to oxidative and genotoxic stress in neuronal-like cells triggered by elevated homocysteine concentration (Curro et al., 2014). It has also been shown that homocysteine, besides acting as a partial agonist at glutamate receptors also acts as partial antagonist of glycine co-agonist site of the NMDA receptor. In the presence of normal glycine levels and normal physiological conditions homocysteine does not cause toxicity below millimolar concentrations. However in case of a head trauma or stroke, there is an elevation in glycine levels in which instance the neurotoxic effect of homocysteine as an agonist outweighs its neuroprotective antagonist effect. This may cause neuronal damage via calcium ion influx or free radical generation (Carmel, Jacobsen, Carmel & Jacobsen, 2001).

In this study, Homocysteine levels were found to be good predictor of ischemic stroke risk with good sensitivity, specificity and positive predictive value.

So, it was concluded that serum homocysteine levels were found to be significantly elevated in ischemic stroke patients. But, further studies are needed to search for exact causal role of increased homocysteine in ischemic stroke patients with larger sample size. It will be worthwhile to consider folic acid and Vitamin B12 supplementation for secondary prevention in stroke patients having high serum homocysteine levels. And we support consideration of serum homocysteine as a regular and routine screening marker to protect target organ damage.

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