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Original Research Article

Plasma homocysteine levels in Indian patients with acute ischemic stroke

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ABSTRACT

Background: Homocysteine has primary atherogenic and prothrombotic properties. The present study aimed to assess serum homocysteine levels in patients with ischemic stroke and to find association of serum homocysteine levels with various patient related variables.
Methods: This observational study included patients who were admitted with the diagnosis of stroke in Sri Ventateswara Ramnarain Ruia Government General Hospital. Patients were evaluated for risk factors like hypertension, diabetes mellitus and hyperlipidemia. Total homocysteine estimation was done and survival of the patients was assessed at the time of discharge from the hospital.
Results: Most common risk factor for stroke in our study population was dyslipidemia (40%), followed by hypertension (36%). Total homocysteine levels were raised in 92% of the patients. Patients with homocysteine levels less than 15µM/L had lacunar infarcts. Homocysteine levels higher than 100µM/L were found in 18% of the patients and they all had large sized lesions. Significantly higher mean homocysteine levels were found among patients with large lesions (70.15±2.65 vs 21.68±8.02, p value <0.05). Among various risk factors, higher mean homocysteine levels were found to be associated with dyslipidemia (p value <0.05). No association between hypertension, diabetes mellitus or smoking history was found with higher homocysteine levels. Patients who survived had significantly lower homocysteine levels as compared to non survivors (39.3±19.84 vs 100±18.82, p value<0.001).
Conclusions: Further studies are needed on homocysteine and stroke fur using homocysteine as screening test and for initiation of preventive therapy of stroke based on homocysteine levels.

Keywords: Homocysteine, Ischemic stroke, Stroke

INTRODUCTION

Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. Homocystinuria or severe hyperhomocysteinemia is a rare autosomal recessive disorder characterized by severe elevations in plasma and urine homocysteine concentrations. Clinical manifestations of homocystinuria include developmental delay, osteoporosis, ocular abnormalities, thromboembolic disease, and severe premature atherosclerosis. Less marked elevations in plasma homocysteine are much more common, occurring in 5 to 7% of the population.[1] Although un-associated with the clinical stigmata of homocystinuria, mounting evidence suggests that moderate hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular

disease and for recurrent venous thromboembolism. Homocysteine has primary atherogenic and prothrombotic properties. Histopathologic hallmarks of homocysteine-induced vascular injury include intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation, and the formation of platelet-enriched occlusive thrombi.[2]

Stroke is a leading cause of mortality and subsequent serious long-term disability among patients who survive the episode. Studies have shown that high plasma homocysteine levels are an independent risk factors for cerebrovascular atherosclerotic occlusive disease.[3] Animal experiments have shown that plasma homocysteine, by releasing endothelial nitric oxide, can result in endothelial cell injury and functional abnormalities.[4] The present study aimed to assess serum homocysteine levels in patients with ischemic stroke and to find association of serum homocysteine levels with various patient related variables.

METHODS

This observational study included patients who were admitted with the diagnosis of stroke in Sri Ventateswara Ramnarain Ruia Government General Hospital. Patients with age greater than 18 years, with first ever episode of stroke, documented with computed tomography scan which was taken within 48hours of onset of symptoms were included in the study. Patients who had recurrent stroke, with subdural hematomas, intracranial tumours or other space occupying lesions, meningitis, brain abscesses or other intracranial infections were excluded from the study. We also excluded patients with head injury, post-operative patients and neoplasia, rheumatoid arthritis, ankylosing spondylitis, chronic infection and inflammatory conditions. Patients who met the inclusion and exclusion criteria were included in the study after obtaining their or their attendant's informed written consent. The study was approved by the institutional ethics committee. All the patients included in the study were examined thoroughly by a senior physician and patient's history and findings of clinical examination were noted using a pre-tested, semi-structured questionnaire. Patients were evaluated for risk factors like hypertension, diabetes mellitus and hyperlipidemia. Investigations were ordered as per the management protocol by treating physician. For total homocysteine estimation blood sample was collected and with in 30 minutes plasma was separated and stored at -20°C. Testing was done using competitive immunoassay method using Immulite 1000 auto analyser and commercial kits. The normal range of plasma homocysteine was taken as 5-15µmol/L based on previously published literature.[5] Survival of the patients was assessed at the time of discharge from the hospital.

Data was coded and analysed using SPSS software (version 21 for Windows). Qualitative data were expressed as numbers and percentages and quantitative numbers as mean and standard deviation. Kolmogorov-Smirnov test was applied to test for normal distribution of data. To compare mean values of homocysteine a Student's t-test was performed for normal data and Mann-Whitney test for not normal data, p-value less than 0.05 was considered significant.

RESULTS

The study group consisted of 50 patients with cerebrovascular stroke. The maximum number of cerebrovascular accidents were found in age groups 51-60 years and 61-70 years which contribute 68% of the study group (Table 1).

Table 1: Distribution of patients according to their baseline characteristics.

Variable	n (%)
Age distribution (in years)	
41 to 50	13 (26%)
51 to 60	17 (34%)
61 to 70	17 (34)
71 to 80	02 (04%)
More than 80	01 (02%)
Gender distribution	
Males	36 (72%)
Females	14 (28%)
Risk factors	
Hypertension	18 (36%)
Diabetes mellitus	13 (26%)
Smoking	16 (32%)
Dyslipidemia	20 (40%)
Clinical features	
Hemiplegia	37 (74%)
Aphasia	29 (58%)
Drowsy	21 (42%)
Unconscious	07 (14%)
Convulsions	07 (14%)
Vomiting	02 (04%)
Ataxia	01 (02%)
Size of lesion	
Small (< 2 cm)	18 (36%)
Large (>2 cm)	32 (64%)
Homocysteine levels	
< 15µM/L	04 (08%)
15 to 30µM/L	12 (24%)
31 to 100µM/L	25 (50%)
>100µM/L	09 (18%)

In the study, 72% were males and 28% were females. None of the subject was below the age of 40 years. Most common risk factor in our study population was dyslipidemia (40%), followed by hypertension (36%). Least common risk factor was diabetes mellitus (26%). We observed that the most common presenting symptom was hemiplegia which was present in 74% of the patients

and speech disturbance in the form of dysarthria or aphasia in 58% of the patients. Altered sensorium was observed in 56% of the patients. Least common presentation was vomiting and ataxia. Small infarcts were found in 36% of the patients and 64% had large infarcts (>2cms). Homocysteine levels less than 15µM/L were considered normal. In our study group, homocysteine levels were raised in 92% of the patients. Patients with homocysteine levels less than 15µM/L had lacunar infarcts. Homocysteine levels higher than 100µM/L were found in 18% of the patients and they all had large sized lesions. Significantly higher mean homocysteine levels were found among patients with large lesions (70.15±2.65 vs 21.68±8.02, p value <0.05) (Table 2). Among various risk factors, higher mean homocysteine levels were found to be associated with dyslipidemia (p value <0.05). No association between hypertension, diabetes mellitus or smoking history was found with higher homocysteine levels. Patients who survived had significantly lower homocysteine levels as compared to non survivors (39.3±19.84 vs 100±18.82, p value <0.001).

Table 2: Association of mean levels of homocysteine with various patient related variables.

Variable	Mean homocysteine levels (in µM/L)	p value
Size of lesion		
Small (< 2cm)	21.68±8.02	<0.05
Large (> 2 cm)	70.15±2.65	
Hypertension		
Yes	55.11±33.37	> 0.05
No	51.31±31.61	
Diabetes mellitus		
Yes	45.23±33.19	> 0.05
No	55.29±31.57	
Dyslipidemia		
Yes	66.15±34.36	<0.05
No	43.70±27.29	
Smoking		
Yes	55.37±26.02	> 0.05
No	51.41±34.70	
Survived		
Yes	39.3±19.84	<0.001
No	100±18.82	

DISCUSSION

The present study assessed the homocysteine levels of 50 patients with ischemic stroke. The study found significantly higher mean homocysteine levels among patients with large infarcts, history of dyslipidemia, and those who did not survive. Homocysteine is a nonprotein amino acid that is homologous to cysteine. It is not obtained from food directly but biosynthesized from methionine through several steps. homocysteine can be recycled back to methionine or converted to cysteine.[6] Homocysteine metabolism pathways have several steps that require pyridoxine, folic acid, or methylcobalamin as coenzymes. Vitamin B deficiency is one of the possible hindrances that can affect homocysteine metabolism and cause hyperhomocysteinemia. Hyperhomocysteinaemia may be caused by genetic defects of enzymes, or their cofactors or co-substrates, involved in the re-methylation or trans-sulphuration of homocysteine; vitamin deficiency (folate, vitamin B6, vitamin B12); renal failure; and various other diseases and medications. In contrast, L-thyroxine and insulin appear to lower total homocysteine plasma levels.[7] The hypothesis that high levels of total homocysteine may lead to atherosclerosis evolved many decades ago when it was first observed that patients with homocystinuria and extremely high plasma levels of total homocysteine had a high incidence of vascular disease and premature deaths from myocardial infarction.[8] Over the years, numerous studies have demonstrated the association of hyperhomocysteinaemia with different vascular diseases.[9]

Many systematic reviews and meta-analysis have demonstrated that there is a direct association between higher levels of total homocysteine and cerebral, coronary and peripheral vascular diseases.[10,11] Furthermore, specific etiological types of ischemic strokes are associated with a high total homocysteine level. High homocysteine levels have been found associated with stroke caused by large artery disease and less so with small artery disease, but not cardioembolic or other non-atherosclerotic causes of stroke.[12] Additionally, a greater risk of atherosclerotic disease is found with a higher levels of total homocysteine levels, so the relationship is dose-related, strong and biologically plausible. However, such associations have been found in studies using less robust methodologies, most of the prospective cohort studies demonstrated a weak association.[13] Moreover, the temporal relationship between the onset of elevated total homocysteine levels and the onset of stroke is still not completely understood. Some studies suggest that elevated total homocysteine levels may be an acute-phase reactant that rises after the stroke or other vascular event in response to tissue damage or tissue repair.[14]

There are a few limitations of this study. Firstly, only single measurement of homocysteine was made rather than serial measurements. Secondly, we did not adjust the analysis for potential confounders such as low density lipoprotein, blood markers of the pathological processes in acute ischemic stroke such as inflammation, hemostasis, neuronal or glial injury and cardiac function. Finally, the small sample size from a single centre might limit the generalizability of the results of this study.

CONCLUSION

Authors found significantly higher mean homocysteine levels among patients with large infarcts, history of dyslipidemia, and those who did not survive. Further

studies are needed on homocysteine and stroke fur using homocysteine as screening test and for initiation of preventive therapy of stroke based on homocysteine levels. Additional well-designed prospective studies regarding are needed to ascertain the relationship between homocysteine levels and the risk of stroke subtypes.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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