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Role of homocysteinemia in young ischemic stroke and its radiological correlation

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Abstract:
Hyperhomocysteinemia is a potentially modifiable risk factor for ischemic stroke, but its relationship with radiological severity in young adults remains incompletely understood. This prospective observational study evaluated 100 patients aged 18–45 years with imaging confirmed acute ischemic stroke through clinical assessment, fasting serum homocysteine estimation and neuroimaging. Hyperhomocysteinemia was present in 58% of patients and was significantly associated with anterior circulation infarcts, larger infarct size, multiple infarcts, large vessel occlusion and higher National Institutes of Health Stroke Scale scores ($p<0.05$), indicating greater radiological severity. Elevated serum homocysteine levels were strongly associated with more extensive ischemic brain injury and increased stroke severity in young adults. These findings advance knowledge by supporting serum homocysteine as a clinically relevant biomarker for risk stratification and targeted preventive strategies in young patients with ischemic stroke.

Keywords: Young ischemic stroke, hyperhomocysteinemia, homocysteine, magnetic resonance imaging, computed tomography (CT), radiological correlation, stroke severity

Background:
Stroke continues to be one of the most important causes of death and chronic disability globally and a serious public health issue. Ischemic stroke is generally thought of as a disorder of older children and strokes occurring in the young years have increased over the past few decades. Young onset stroke is an emerging and escalating problem with a significant impact in terms of disability adjusted life years (DALYs), morbidity and early mortality, particularly affecting those at their most productive years **[1].** Young ischemic stroke, typically defined as stroke occurring before the ages of 45–50, presents with different underlying causes, clinical manifestations and outcomes than stroke **[2]**. However, data-driven analyses suggest that the upper age threshold for young ischemic stroke may vary by sex and population, with estimates of 54 years in women and 52 years in men in one US cohort **[3]**. Younger patients often have unusual precipitating factors, such as inherited thrombophilia, autoimmune conditions, arterial dissection, cardioembolism and metabolic disorders, as well as common risk factors that include hypertension, diabetes mellitus, smoking and dyslipidaemia. Of these, hyperhomocysteinemia has become a potentially reversible risk factor of prematurely occurring cerebrovascular disease **[4].** Homocysteine is an amino acid with a sulphur group that is produced during the metabolism of methionine. Possible causes of high plasma homocysteine are deficiency of folate, B6, B12, renal failure, genetic polymorphisms, medications and lifestyle. Hyperhomocysteinemia is associated with endothelial dysfunction, oxidative stress, vascular inflammation and thrombosis leading to an increased risk of ischemic stroke. A recent systematic review and meta-analysis confirmed the association between elevated homocysteine levels and higher risk of ischemic stroke, independently of other risk factors, so that this could serve as a marker and therapeutic target for upcoming cases of stroke **[2].** The increasing multimodal use of brain imaging has improved the diagnosis and management of acute ischemic stroke **[5]**. Symptomatic relief, accomplished by the expedient use of computed tomography (CT), magnetic resonance imaging (MRI) and vascular imaging, to facilitate timely reperfusion therapy and outcomes, is equally important as recommended by current American Heart Association/American Stroke Association guidelines, as is the identification and management of modifiable vascular and metabolic risk factors, including hyperhomocysteinemia, for secondary prevention **[6].** Risk assessment has taken on a much greater personal significance in the prevention of stroke. Biochemical markers, including hyper-homocysteinemia may enable targeted interventions with vitamin supplementation and lifestyle modification, which can help to reduce recurrent cerebrovascular events. Clinical, laboratory and radiological cross-correlation was previously highlighted to enhance the understanding of stroke mechanisms and to assist tailoring stroke treatment in patients **[7].** However, the World Stroke Organization Global Stroke Fact Sheet 2025 noted the rising disease burden in youth, especially those in LMICs and the necessity of uncovering novel stroke biomarkers linked to disease severity and prognosis early **[8].** Therefore, it is of interest to evaluate the importance of hyperhomocysteinemia in the young ischemic stroke patient and its relationship to radiological characteristics.

Materials and Methods:
Study design:
This prospective, observational, hospital based study aimed to assess the relationship of serum homocysteine level to radiological results in young acute stroke patients.

Study setting:
The study was completed in the Dept. of General Medicine with collaboration of the Department of Neurology and the Dept. of Radio diagnosis of a Tertiary care teaching hospital with the permission of the Institutional Ethics Committee.

Study duration:
All consecutive patients suffering from acute ischemic stroke were recruited and assessed for 24 months.

Study population:
This study included young adult patients (aged <65 years) who were admitted with a diagnosis of acute ischemic stroke confirmed by neuroimaging.

Sample size:

Patients who met the eligibility criteria were collected consecutively and 100 consecutive patients were used for the study.

Inclusion criteria:
[1] Patients aged 18–45 years.
[2] First stroke (acute ischemic stroke) diagnosed with CT scan or MRI of the brain.
[3] Symptoms of neurological involvement within 7 days of onset;
[4] Patients who can sign informed consent form.

Exclusion criteria:
[1] Age>45 years.
[2] Hemorrhagic stroke.
[3] Raised pressure of blood in a vein within the brain.
[4] Previous stroke or transient ischaemic attack (TIA) History
[5] Chronic kidney disease, chronic liver disease, hypothyroidism or cancer.
[6] Patients who were taking folic acid supplements, vitamin B6 or B12 supplements for the 3 months prior to the study.
[7] Pregnancy.
[8] Patients unwilling to participate.

Clinical evaluation:
Socio-demographic details and vascular risk factors, smoking history, alcohol history, hypertension history, diabetes mellitus history, dyslipidaemia and family history of stroke, history of medication and duration of symptoms were collected in detail. All participants had a thorough general and neurological examination.

Laboratory investigations:
Venous samples were taken following 12 hours of fasting. Complete blood count and blood glucose, renal function tests, liver function tests, lipid profile, serum electrolytes, serum vitamin B12 and folate levels were performed routinely as indicated. The measurement of serum homocysteine was performed by standardized chemiluminescent immunoassay method. Hyperhomocysteinemia was considered to be a fasting homocysteine level >15 µM/L.

Radiological assessment:
Non-contrast computed tomography (CT) brain at admission was obtained in all patients; MRI brain with diffusion weighed images was obtained at admission, when possible. When indicated clinically, MR angiography was used or CT angiography. The following radiological parameters were evaluated:
[1] Site of infarction.
[2] Vascular territory involved.
[3] Patients with cortical versus subcortical infarction.
[4] Infarct size.
[5] Multiple: two or more infarcts.
[6] Large-vessel occlusion.
[7] Small vessel disease changes
[8] Abnormalities of the arteries in the neck (carotid) or brain (intracranial).

Radiological findings were evaluated by an experienced radiologist, blind to the serum homocysteine concentration.

Outcome measures:
Primary outcome:
A correlation between serum homocysteine level and young ischemic stroke

Secondary outcomes:
[1] Correlation of serum homocysteine level with location of the infarct.
[2] Correlation with the infarct size and vascular territory.
[3] Association between hyperhomocysteinemia and the radiological severity.
[4] Association of homocysteine blood levels with neurological deficit on admission.

Statistical analysis:
The data was entered in computers using the Microsoft excel software with the intent of analysing it with IBM SPSS statistics version 26.0. Data for continuous variables were reported as mean with SD and data for categorical variables as frequency and percentage. The continuous variables were compared using the Student's t-test or Mann- Whitney U test while the categorical variables were compared by the Chi square test or Fisher's exact test. Pearson's or Spearman's correlation coefficient was used to evaluate the correlation between serum homocysteine levels and radiological variables. A p value was considered statistically significant if < 0.05.

Results:
A total of 100 young patients with acute ischemic stroke were included in the study. The age of the study population was an average of 36.8 ± 6.4 years; most of the cases were males. Hyperhomocysteinemia (Serum homocysteine level > 15µmol/L) was detected in 58% of patients. Brain imaging of patients with elevated homocysteine showed a greater incidence of large infarcts, anterior circulation involvement and multiple infarcts than did patients with normal homocysteine levels. The majority of patients were aged 36 to 45 (54%) followed by 26 to 35 (32%) and 18 to 25 (14%) and 68% of the patients were males. Elevated homocysteine is a relatively common biochemical abnormality as hyperhomocysteinemia was noted in 58% of young ischemic stroke patients **(Table 1).** Anterior circulation infarcts (67%) were more common than posterior circulation infarcts. Medium-sized infarcts were most common with 25% having large infarcts and 22% multiple infarcts **(Table 2).** Anterior circulation infarction was more frequent among patients with hyperhomocysteinemia than among those with normal homocysteine levels (75.9% vs 54.8%, $p = 0.028$). Large infarcts (36.2% vs 9.5%, $p = 0.002$), multiple infarcts (31.0% vs 9.5%, $p = 0.011$), large-vessel occlusion (34.5% vs 16.7%, $p = 0.046$), and small-vessel disease (25.9% vs 9.5%, $p = 0.037$) were

also more frequent in the hyperhomocysteinemia group **(Table 3).** Mean serum homocysteine levels increased across NIHSS categories, from 13.8 ± 3.9 µmol/L for NIHSS ≤5 to 24.1 ± 6.2 µmol/L for NIHSS >10 ($p < 0.001$). Levels also increased across infarct-size categories, from 14.2 ± 4.1 µmol/L for small infarcts to 25.4 ± 6.3 µmol/L for large infarcts ($p < 0.001$) **(Table 4).**

Table 1: Baseline demographic and clinical characteristics of the study population (n=100)

Variable	Number	Percentage (%)
Age Group (years)		
18–25	14	14
26–35	32	32
36–45	54	54
Gender		
Male	68	68
Female	32	32
Hypertension	34	34
Diabetes mellitus	18	18
Smoking	41	41
Alcohol consumption	29	29
Dyslipidemia	26	26
Family history of stroke	12	12
Hyperhomocysteinemia (>15 µmol/L)	58	58

Mean serum homocysteine: 18.9 ± 6.7 µmol/L

Table 2: Radiological characteristics of ischemic stroke

Radiological Variable	Number	Percentage (%)
Vascular territory		
Anterior circulation	67	67
Posterior circulation	33	33
Site of infarction		
Cortical	42	42
Subcortical	38	38
Cortico-subcortical	20	20
Infarct size		
Small	35	35
Medium	40	40
Large	25	25
Multiple infarcts	22	22
Large vessel occlusion	27	27
Small vessel disease changes	19	19

Table 3: Correlation of serum homocysteine levels with radiological findings

Radiological finding	Hyperhomocysteinemia (n=58)	Normal Homocysteine (n=42)	p value
Anterior circulation infarct	44 (75.9%)	23 (54.8%)	0.028*
Posterior circulation infarct	14 (24.1%)	19 (45.2%)	
Large infarct	21 (36.2%)	4 (9.5%)	0.002*
Multiple infarcts	18 (31.0%)	4 (9.5%)	0.011*
Large vessel occlusion	20 (34.5%)	7 (16.7%)	0.046*
Small vessel disease	15 (25.9%)	4 (9.5%)	0.037*

**Chi-square test; p<0.05 considered statistically significant.*

Table 4: Correlation between serum homocysteine levels and stroke severity

Variable	Mean Homocysteine (µmol/L)	p value
NIHSS ≤5	13.8 ± 3.9	
NIHSS 6–10	17.6 ± 4.5	
NIHSS >10	24.1 ± 6.2	<0.001*
Small infarct	14.2 ± 4.1	
Medium infarct	18.1 ± 5.0	
Large infarct	25.4 ± 6.3	<0.001*

Statistical test: One-way ANOVA.

Discussion:

In the present study, the authors investigate the value of hyperhomocysteinemia in a younger cohort of acute ischemic stroke patients and its relationship to radiological assessments. Hyperhomocysteinemia was seen in 58% of the patients and was significantly linked to greater neurological severity, multiple infarcts, large vessel occlusion, anterior circulation involvement and larger infarct size. The results are consistent with the emerging literature indicating that hyperhomocysteinaemia is a significant potentially modifiable risk factor in young people with ischaemic stroke. In a thrombectomy-treated cohort of patients younger than 50 years, Weber *et al.* reported sex-related differences in stroke aetiology and reperfusion outcomes, highlighting the clinical heterogeneity of young-onset stroke **[9]**. Mild elevation of homocysteine was also reported to be significantly related to ischemic stroke in young Asian patients, especially those who had had spontaneous cervical artery dissection, by Lin *et al.* **[10].** In a similar vein, Spence pointed out that Hyperhomocysteinemia causes oxidative stress, endothelial damage, inflammation and thrombosis, making people more vulnerable to ischemic stroke, especially at moderate levels. He also pointed out that in individual patients the risk of recurrence of stroke may be reduced through homocysteine lowering by folate and B-vitamin supplementation **[11].** In the present study, hyperhomocysteinemia was observed in a high prevalence, which is compatible with the previous reports assessing the prevalence in young stroke patients. Hasan *et al.* noted that metabolic abnormalities which can be reversed, such as elevated homocysteine, are important to detect when evaluating young ischemic stroke and noted that failure to recognize them may lead to suboptimal treatment, which increases the likelihood of having a recurrent cerebrovascular event; prescriptive data in our study support this finding **[12].** In a seven-year follow-up study, diabetes was independently associated with poor functional outcome in young stroke patients, and recurrent vascular events were associated with poor outcome among those with diabetes **[13]**. Divišová *et al.* also found that young patients with hypertension had more recurrent ischemic events during follow-up, although hypertension was not an independent predictor in their multivariable model **[14]**. Wardlaw *et al.* also mentioned that endothelial dysfunction and vascular injury contribute to cerebral small vessel disease, in keeping with the higher rate of small vessel disease changes among patients with an elevated homocysteine that was observed prescriptively within our study **[15].** Deng *et al.* reported cerebral microbleeds in 16% of young ischemic stroke patients and found associations with hypertension, lower estimated glomerular filtration rate, and moderate-to-severe white matter hyperintensity **[16]**. This indicates that the main determinants of ischemic stroke in most COVID-19 patients are still the conventional vascular and metabolic risk factors, highlighting the on-going significance of the evaluation of biochemical markers, especially in patients younger than age 55 who have fewer related cardiovascular risk factors, in the context of COVID-19 **[17].** A person's susceptibility to homocysteine also has a strong influence. The clinical relevance of the polymorphisms of the MTHFR gene was discussed by Araszkiewicz *et al.* who concluded that decreased

enzyme activity leads to raised plasma concentrations of homocysteine, which leads to an elevated risk of thrombotic and cerebrovascular diseases. They propose that selected young hyperhomocysteinemic stroke survivors should be considered for genetic assessment **[18].** Niazi *et al.* found it to be common among youths with ischemic stroke and showed that increased homocysteine was correlated with poor early neurological outcome. The same was also seen in the current study, in which the NIHSS scores and the numbers of infarcted areas were significantly higher in patients with hyperhomocysteinemic, as revealed by neuroimages **[19].** Radiological correlation is becoming a voice of increasing importance in stroke severity and treatment decisions. Campbell *et al.* showed that accurate brain imaging modalities identified the vascular occlusion and infarct extent, so that we can improve therapeutic planning and their prognosis **[20].** In more recent studies, Al-Salahat *et al.* further underscored the growing contribution of the advanced CT and MRI markers in assessing infarct burden, collateral circulation and tissue viability in acute ischemic stroke, thereby emphasizing radiologic correlation as part of stroke management today **[21].** Therapeutic intervention is clinically relevant since hyperhomocysteinemia is potentially reversible. Based on this work, folic acid supplementation could be a contributing factor in cardiovascular and cerebrovascular risk protection, especially for patients who have high baseline concentrations of homocysteine, while enabling early detection or hyperhomocysteinemia and therefore the ability to do preventive action with folic acid supplementation **[22].** A case report by Rafay *et al.* describes a young patient with hyperhomocysteinemia-associated ischemic stroke, but this single case cannot establish the effectiveness of vitamin therapy **[23]**. To support this idea, Ghose *et al.* showed a significant relationship between increased homocysteine levels, low levels of B12 and folate and the presence of ischemic stroke in India. They also confirm the necessity of screening nutritional metabolic abnormalities as a component of the complete evaluation of young patients with ischemic stroke, which further highlights the role of these abnormalities in this patient population **[23].**

Conclusion:

Young ischemic stroke patients had a very high prevalence of hyperhomocysteinemia, which was found to be significantly associated with larger infarct size, anterior circulation involvement, multiple infarcts and higher neurological severity. The results indicate that high homocysteine level was a significant modifiable risk factor and could be a potential marker for radiographic severity in young ischemic stroke. Seeking out baseline tests for hyperhomocysteinemia may make early therapy more possible and aid in secondary stroke preventions.

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